FABRICATION AND CHARACTERIZATION OF TASTE MASKED POROUS TABLETS OF LOSARTAN POTASSIUM BY SUBLIMATION TECHNIQUE

Dissertation Submitted to

The Tamil Nadu Dr. M.G.R. Medical University

Chennai - 600 032

In partial fulfillment for the award of Degree of

MASTER OF PHARMACY

[PHARMACEUTICS]

submitted by

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MAY-2012

CERTIFICATE

This is to certify that the research work entitled "**FABRICATION AND CHARACTERIZATION OF TASTE MASKED POROUS TABLETS OF LOSARTAN POTASSIUM BY SUBLIMATION TECHNIQUE"**Submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **R.A.S.JAMUNAVATHY** (**Register No: 26106002)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

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ACKNOWLEDGEMENT

It's my priviledge and honor to extend my profound gratitude and thanks to his Holiness **ARULTHIRU AMMA** for his ever growing Blessings in each step of the study.

With great respect and honor, I extend my thanks to our Vice president **THIRUMATHI LAKSHMI BANGARU ADIGALAR,** ACME trust, Melmaruvathur for her excellence in providing skillful and compassionate spirit of unstinted support to our department for carrying out research work entitled **"FABRICATION AND CHARACTERIZATION OF TASTE MASKED POROUS TABLETS OF LOSARTAN POTASSIUM BY SUBLIMATION TECHNIQUE"**

I concede my in most special gratitude and thanks to **Prof. K. SUNDARAMOORTHY, B.Sc., M.Pharm.,** Professor, Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, for his active guidance throughout my work.

I owe my sincere thanks with bounteous pleasure to **Prof.(Dr.)T.VETRICHELVAN, M.Pharm., Ph.D.,** Principal, Adhiparasakthi College of Pharmacy, without his encouragement and supervision it would have been absolutely impossible to bring out the work in this manner.

I have great pleasure in express my sincere heartfelt thanks to D**r. S. SHANMUGAM, M.Pharm., Ph.D., Assistant Professor, Mr. T. AYYAPPAN, M.Pharm Senior Lecturer** and **Mr. A. UMAR FARUKSHA, M.Pharm., Lecturer,** Department of pharmaceutics, **Dr. D. NAGAVALLI, M.Pharm., Ph.D., Professor** and **Mr. K. ANANDHA KUMAR, M.Pharm., Assistant Professor,** Department of Pharmaceutical Analysis, and

my special thanks to **Mr.M.SUGUMARAN, M.Pharm., Professor,** Department of pharmaceutical Chemistry, for encouragement and support for the successful completion of this work.

My sincere and heart filled thanks to all our lab technicians **Mrs. S. KARPAGAVALLI,D. Pharm.,** and **Mr.M.GOMATHI SHANKAR,D. Pharm.,** for their kind help throughout this work.

I am indeed very much thankful to our college librarian **Mr.M.SURESH, M.L.I.S.,** for providing all reference books for the completion of this project. A special word of thanks to my other friends for their timely help during the course of my work.

R.A.S.JAMUNAVATHY

Dedicated To

My Beloved Parents

&

My beloved teachers...✍

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LIST OF ABBREVIATIONS USED

CP	----	Crosspovidone
PVP	----	Polyvinylporrolidone
MDT	----	Mouth Dissolving Tablets
MDDS	----	Mouth dissolving drug delivery systems
UV	----	Ultra Violet
HCl	----	Hydrochloric acid
µg	----	Microgram
λmax	----	Absorption maximum
ml	----	Milliliter
N	----	Normality
mg	----	Milligram
nm	----	Nanometer
FTIR	----	Fourier Transform-Infra Red Spectroscopy
DSC	----	Differential Scanning Calorimetry
TLC	----	Thin Layer Chromatography
HPLC	----	High Perfomance Liquid Chromatography
FDT	----	Fast Dissolving Tablets
ODTs	----	Orally Disintegrating Tablets
cm	----	Centimeter
%	----	Percentage
RH	----	Relative Humidity
USP	----	United State Pharmacopoeia
IP	----	Indian Pharmacopoeia
t	----	Time
w/v	----	weight/volume

gm	----	Grams
RPM	----	Revolutions per Minute
mm	----	Millimeter
Sl. No.	----	Serial Number
°C	----	Degree Celsius
GIT	----	Gastrointestinal Tract
SD	----	Standard Deviation
DE	----	Dissolution Efficiency

INTRODUCTION

1. INTRODUCTION

1.1. GENERAL INTRODUCTION: *(Dhanyakumar D. C.,2010; Bandari Suresh, 2008 ,N.K. Jain, 2008; Kuchekar B.S. et al., 2003; Yie W. Chien, 2009)*

New drug-delivery technologies are often championed by contract manufacturing organizations. For new technologies that provide significant clinical as well as financial value, research and innovation in the contract manufacturing and pharmaceutical segments lead to the emergence of numerous competing versions of the technologies. Such a technology evolution has been evident for Orally Disintegrating Tablets . Designed to disintegrate rapidly on contact with saliva and enable oral administration without water or chewing, these formulations offer increased convenience and ease of administration with the potential to improve compliance, particularly in certain populations where swallowing conventional solid oral-dosage forms presents difficulties.

The Zydis (Catalent Pharma Solutions, Somerset, NJ) lyophilization technology provided the first approved Oral disintegrating tablets. (Claritin Reditabs, Schering Plough, Kenilworth, NJ) in the United States in 1996.

Oral route of drug administration have wide acceptance up to 50 - 60% of total dosage forms. Solid dosage forms are popular because of

1) Ease of administration
2) Accurate dosage
3) Self – medication
4) Pain avoidance
5) Patient compliance

The most popular solid dosage forms are being Tablets and Capsules; one important drawback of these dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablets when water is not available, in the case of motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic conditions and bronchitis. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted great deal of attention.

Orodispersible Tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.Orodispersible Tablets are also called as Mouth-dissolving tablets, Melt-in-mouth tablets, Fast dissolving tablets, Rapimelts, Porous tablets, Quick dissolving etc.

Orodispersible tablets are those when put on tongue, disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed directly into the systemic circulation through the (oral) mucosa of mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

The advantages of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics. Their growing importance was underlined recently when European Pharmacopoeia adopted the term “Orodispersible tablet” as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. Latest era is an era of Novel Drug Delivery System. Formulation and

Research is oriented towards increasing patient compliance, so the product development came on to screen. Product development has assured enormous significant in the modern pharmaceutical industry particularly as an impact of General Agreement on Trade and Tariff agreement and globalization as well as Patenting compulsions. Product development for well established bioactives (Drugs) is a highly rewarding proposition as this may extend the therapeutic life of such agents at a substantially low investment. Availability of several drugs as modified release dosage forms is one glaring example. For the last two decades, there has been enhanced demand for more patient compliance dosage forms. As a result, the industry sector for this area is approximately $14.20 billion in 1995 and is expected to grow to $60 billion annually (from industry reports). Recent advances in Novel Drug Delivery System aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve the better patient compliance.

Oral Drug Delivery has been the most extensively utilized route of administration for decades among all the routes that have been intended for the systemic deliverance of drugs by various pharmaceutical products of different dosage forms. The oral route achieved such fame due to its reward like self medication, ease of administration, non invasive, less expensive, patient compliance, versatility etc.

Drug delivery through the oral mucosa is a capable route, when one needs to attain a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism .Thus, there is a growing interest in developing alternative dosage forms, i.e. orally fast disintegrating tablets, which allow a rapidly dissolving drug to absorb

directly into the systemic circulation through the oral mucosa. These kinds of dosage forms are also convenient for children, elderly patients with swallowing difficulties, and in the absence of potable liquids. However, in addition to formulation considerations, the properties of the active compound have to be appropriate in order to achieve drug delivery into systemic circulation after intraoral administration. The drug has to be soluble, fast dissolving and stable; and this might represent a hindrance for lipid soluble drugs. Due to the small volume of saliva in the oral cavity, the therapeutic dose of an intraoral drug must be relatively small.

Dysphagia is common problem for children due to their under developed muscular and nervous systems. The uptake of traditional tablets in the cases like motion sickness, sudden episodes of allergic attacks or coughing or during unavailability of water is difficult. The different studies on the dysphagia showed that "26% of 1576 patients experienced difficulty in swallowing tablets and an estimated 35% of general population, and an additional 30 - 40% of elderly institutionalized patients and 18 - 22% of all people in long term care facilitates" are sufferers from dysphagia.

To accomplish above medical requirements, formulators have steadfast significant attempt for developing a novel type of dosage form for oral administration, known as the Immediate Release/ Fast Dissolving/ Oral Disintegrating Tablets and films. These dosage forms are most preferable for over the counter market.

1.2. ORAL DISINTEGRATING TABLETS (ODTs): *(Suresh Bandari et al., 2008; Panigrahi D. et al., 2005; Shastry C.S. et al., 2004)*

US Food and Drug Administration defined Orally Disintegrating Tablets as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually with in a matter of seconds, when placed upon tongue".

Recently European Pharmacopoeia also adopted the term 'Orodispersible Tablet' as a "Tablet that is to be placed in the mouth where it disperses readily and with in 3 minutes in mouth before swallowing".

The US Food and Drug Administration 2008 publication of Guidance for Industry: Orally Disintegrating Tablets. Three main points stand out in the final guidance, those are as follows,

a. ODTs should have an *in-vitro* disintegration time of approximately 30 s or less (using United States Pharmacopeia Disintegration Test or equivalent).

b. Generally, the ODT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an ODT for both patients and regulators.

The guidance serves to define the upper limits of the ODT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an ODT.

The first developed Oral Disintegrating Tablet was developed in late 1970's by the using of Zydis technology as an alternative to tablets, capsules, and syrups.

1.3. Anatomic and Physiologic Features of the Oral Cavity: *(Anne Waugh, 2006)*

The surface area of the oral mucosa is about 100 cm^2. Three different types of oral mucosa are recognized: the mucosa, the lining mucosa, and the specialized mucosa. The masticatory mucosa, representing 25% of the total oral mucosa, is100–200μm thick and covers the gingiva and the hard palate. It is tightly attached to underlying structures and subjected to abrasion and shear stress during mastication. The lining mucosa (60% of the total oral mucosa) is 500–800μm thick and covers the lips, cheeks, soft palate, lower surface of the tongue and the floor of the oral cavity. The specialized mucosa (15% of the total oral mucosa) is present on the dorsum of the tongue and is involved in taste.

1.2.1. Buccal Epithelium

The buccal epithelium is a non-keratinized stratified squamous epithelium, composed of multiple layers of cells that show different patterns of maturation between the deepest cells and the surface. The basal cells of the buccal epithelium are capable of division and maintain a constant epithelial population as cells move toward the surface. Tissue homeostasis requires differentiation followed by migration and desquamation of the superficial cells. The prickle cells (intermediate layer) accumulate lipids and cytokeratins of low molecular weight that do not aggregate to form filaments. An intracellular lipid portion is packaged in small organelles called membrane-coating granules or lamellar granules. Such granules migrate towards the apical surface of the cell, where their membrane fuses with the cell membrane and

their lipid content is extruded in the extracellular space. The buccal epithelium lacks tight junctions, which are common to intestinal and nasal mucosa, but is endowed with gap junctions, glydesmosomes and hemidesmosomes, which are loose intercellular links. The epithelium rests on the basal membrane, an irregular saliva continuous interface between the epithelium and the connective tissue. The basal membrane anchors the epithelium to the connective tissue and improves the barrier function of the epithelium, preventing large molecules from passing through the oral mucosa.

Although buccal absorption is not the specific goal of oral fast- dissolving tablets, this can occur when the drug is released in the oral cavity in contact with buccal mucosa. The drug transport mechanism through the buccal mucosa involves two major routes:

- Transcellular (intracellular)
- Paracellular (intercellular)

The transcellular route involves passage through the cellular membranes with a polar and a lipid domain, while the paracellular route essentially consists of passive diffusion through the extracellular lipid domain. It is generally recognized that the lipid matrix of the extracellular space plays an important role in the barrier function of the paracellular pathway, especially with compounds that are hydrophilic and have a high molecular weight, such as peptides.

1.3.1. Vascularization of the Oral Mucosa

Arterial, venous and lymphatic capillaries penetrate the multi- layered epithelium, infiltrating the connective tissue. The oral mucosa is primarily supplied by the external carotid artery, which serves the large buccal blood vessels. The floor of the mouth, the root of the tongue and the cheek mucosa are the most highly vascularized areas. Vascular drainage from the oral mucosa is primarily via the lingual, facial and retromandibular veins, which flow together into the internal jugular vein. This is the mechanism responsible for by passing first-pass hepatic metabolism.

1.3.2. Salivary Flow

Saliva is the medium for disintegration or dissolution for drug formulations designed to disintegrate/dissolve in the oral cavity; for this reason, the properties of saliva are crucial to oral fast-dissolving tablets. The saliva is primarily secreted in the oral cavity by parotid, submandibular (submaxillary) and sublingual glands, and also by numerous minor glands. The main constituent of saliva is water (99.5% w/v). The remaining 0.5% w/v consists of dissolved compounds; in fact, saliva is a hypotonic solution (150–200 mOsm) compared with extracellular fluids (300 mOsm). The principal components of saliva are: inorganic electrolytes (0.2% w/v), including sodium, potassium, calcium, magnesium, bicarbonate and phosphates; gases (carbon dioxide, nitrogen, oxygen); nitrogen products such as urea and ammonia; ascorbic acid (vitamin C); creatinine; and mucins (high-molecular-weight glydesmosomes coproteins, which render the saliva viscous and adhesive). Saliva also contains amino

acids and proteins, digestive enzymes (salivary α-amylase [ptyalin], lipase, maltase, and lysozyme with antibacterial activity), proteolytic enzymes (moderate levels of esterase, carbohydrases and phosphatases), serum albumin and immunoglobulins.

Saliva has a weak buffering capacity and its normal pH value is slightly acid (pH 6–7); however, salivary flow pH can range from 5.3 (low flow) to 7.8 (peak flow). The accepted range of normal salivary flow is approximately 0.1–0.2 mL/min, increasing to 7 ml/min upon stimulation. Saliva wets the entire oral cavity and the resulting mucus layer ranges from 1 to 400μm in thickness, forming a physical barrier to drug permeation and a useful substrate for mucoadhesive drug delivery systems.

1.4. SYNONYMS FOR ORAL DISINTEGRATING TABLETS:

1) Oro Dispersible Tablets
2) Porous Tablets
3) Quickly Disintegrating Tablets
4) Rapimelts
5) Mouth Dissolving Tablets
6) Fast Dissolving Tablets
7) Fast Disintegrating Tablets
8) Rapid Dissolving Tablets

1.5. IDEAL CHARACTERISTICS OF ORAL DISINTEGRATING TABLETS:

(Brahmeshwar Mishra et al., 2009)

a)Dosage form should be in a way that it should be taken without water.

b)They should easily disintegrate or dissolve in oral cavity.

c)The method of production need high drug loading.

d)They should produce pleasant mouth feel.

e)They should not leave residue in the oral cavity after administration, as the drug passes into GIT.

f)They should show low sensitivity against environmental circumstances i.e. moisture, temperature etc.

g)Should allow the manufacture for using conventional processing.

h)The packaging of the product should be readily adaptable to the conventional packaging equipment.

i)The packaging of ODT formulation should be at low costs.

j)The cost of the final product should be economical.

1.6. ADVANTAGES OF ORAL DISINTEGRATING TABLET: *(Suresh Bandari et al., 2008, Brahmeshwar Mishra et al., 2009)*

The motivating force in raising an Orally Disintegrating Tablets usage may include one or more of the following advantages,

Patient Compliance: Allow patients to easily take the dosage form any time, any where, for systemic absorption. Medication as "bitter pill" has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs.

Patient Convenience: Enhance convenience to the patients in shipping and administrating these dosage forms particularly when travelling by designing them to taken without water.

Rapid Absorption and Onset of Action: Generate rapid absorption and faster onset of therapeutic efficacy mainly from the rapid disintegration or dissolving dosage forms.

Avoidance of First-Pass Effect: Improve bioavailability owing to partial avoidance of first-pass metabolism resulting from pre gastric absorption.

Elimination of Water/ Improved Stability: Provide an alternative to liquid dosage forms (i.e., syrups, solutions, dispersions) and thereby improve physical/ chemical integrity of the drug.

Product Life-Cycle Management: Broaden the product life cycle by product differentiation by given alternative formulations of the conventional products.

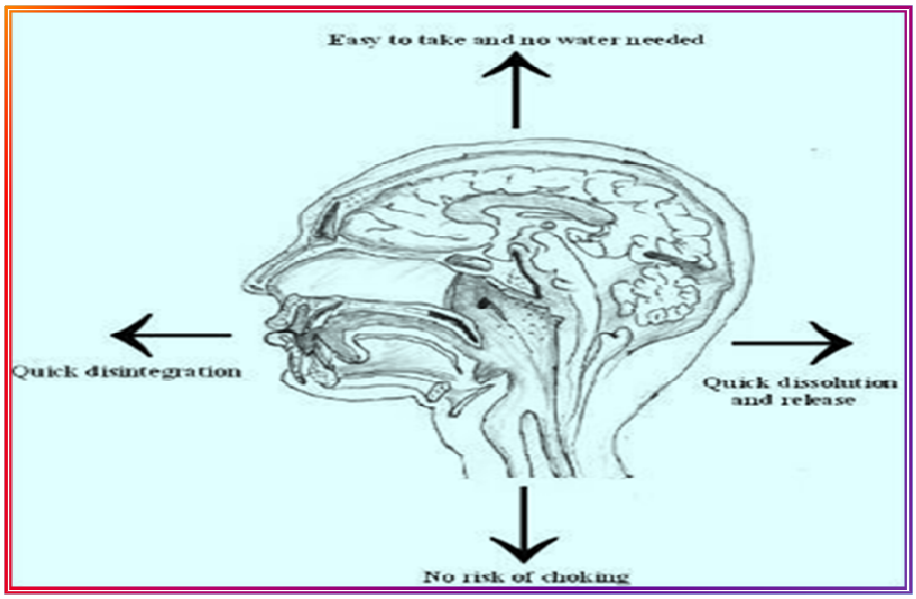


Figure 1.1 Advantages of Oral disintegrating tablets

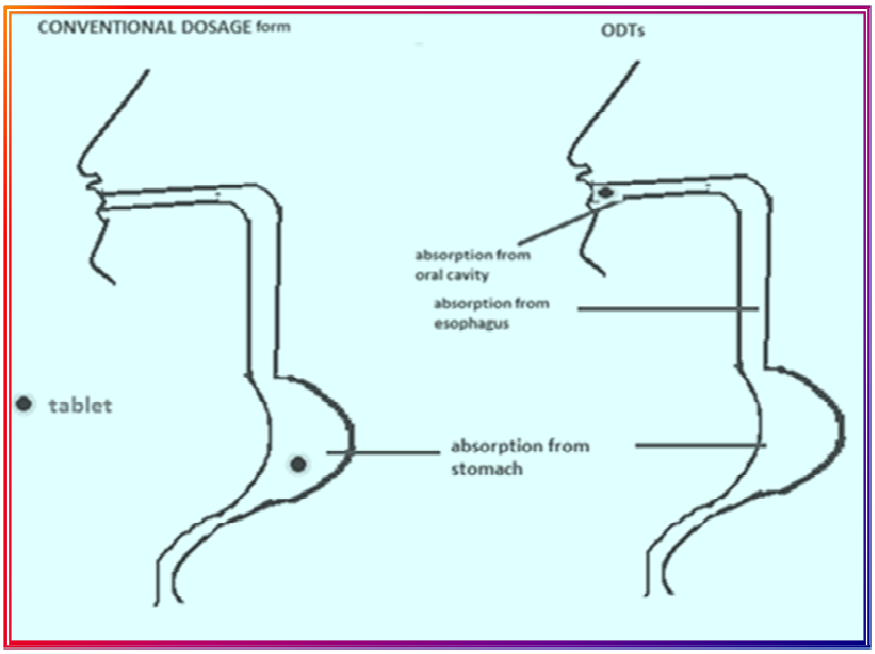


Figure 1.2 How Oral disintegrating tablets Differ from Conventional Tablets

1.7. LIMITATIONS OF ORAL DISINTEGRATING TABLETS: *(Suresh Bandari et al., 2008)*

Certain drugs cannot be formulated as ODTs because of the following limitations:

- The major disadvantage of ODTs is its mechanical strength.
- Several ODTs are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging.

ODTs are very porous and soft molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, require specialized peel-off blister packaging.Bitter drugs or drugs

with a displeasing odor are complicated to formulate as ODTs. Special precautionary measures have to be taken before formulating such type of drugs.

1.8. CHALLENGES TO DEVELOP ORAL DISINTEGRATING TABLETS:

(Suresh Bandari et al., 2008)

1.Achieve rapid disintegration of tablet.

2.Avoid increase in tablet size.

3.Possess sufficient mechanical strength.

4.Leave minimum or no residue in mouth.

5.Protection from moisture.

6.Good package design.

7.Compatible with taste masking technology.

8.Not affected by drug properties.

1.9. LIST OF DRUGS TO BE INCORPORATED IN ORAL DISINTEGRATING TABLETS:

Table 1.1 List of Drugs Suitable for ODTs

CATEGORY OF DRUGS	SOME EXAMPLES
Analgesics	Naproxen, Piroxicom, Sulindac, Ketoprofen
Anthelmentics	Albendazole, Ivermectin, Thiabendazole
Anti- arrhythmic Agents	Amiodarone HCl, Disopyramide, Flecainide acetate
Anti-depressants	Amoxapine, Ciclazindol, Maprotiline HCl
Anti-diabetics	Chlorpropamide, Glibenclamide, Gliclazide
Anti-epileptics	Beclamide, Carbamazepine, Clonazepam, Ethotoin
Anti-hypertensive Agents	Nifedipine, Nimodipine, Phenoxybenzamine HCl
Anti-migraine Agents	Methysergide, Pizotifen Maleate, Sumatriptan

1.10.TECHNICQUES OF ORAL DISINTEGRATING TABLETS FORMULATION:

(Brahmeshwar Mishra et al., 2009)

The fast-dissolving property of the ODTs is attributed to quick ingress of water into tablet matrix resulting in rapid disintegration. Hence, the basic approaches to develop ODTs include:

a) Maximizing the porous structure of the tablet matrix.

b) Incorporating the appropriate disintegrating agent/agents.

Using highly water-soluble excipients in the formulation.

Various manufacturing techniques for ODTs include:

1. Lyophilization
2. Moulding
3. Direct Compression
4. Cotton Candy Process
5. Spray Drying
6. Sublimation
7. Mass Extrusion
8. Nanonization

1.10.1. Lyophilization:

1.The mechanism or process behind the freeze-drying process includes following steps,

3. The water is removed from the preparation by means of sublimation.
4. After water removal the product undergoes to the freezing.

Zydis, Quicksolv and Lyoc technologies used for the preparation of ODTs were come in to screen from this technology basis. Jaccard and Leyder improved

bioavailability of several drugs such as Spironolactone and Trolendomycin by utilizing this lyophilization technique.

1.10.1.1. Zydis Technology:

In present era of in fast-dissolving technology Zydis was the pioneer technology. The technology leads to formation of open matrix of water-soluble or water-dispersible carriers. This matrix will result in a structure with a density that is affected by the amount of active ingredient incorporated. The tridimensional structure leads to formation of solid foam with poor crystalline composition. When it places in the saliva it enters into the matrix through the pores leads to rapid disintegration.

The process of preparation involves the following steps:

Stage 1 - Preparation of an aqueous drug solution or suspension followed by filling the solution in the accurate dose in to the pre-formed blisters.

Stage 2 - This step includes passing of filled blisters into a specially designed cryogenic freezers to undergo cryogenic freezing process to form the tablets with a porous matrix. This formation of the porous matrix leads to rapid disintegration.

After the formation of the porous matrix tablets in the pre formed blisters, these units will move to the large-scale freeze dryers for sublimation process. In this step the majority of the remaining moisture is removed from the tablets.

Stage 3 - Sealing the open blisters using a heat-seal process to ensure stability and protection of the product from varying environmental conditions.

1.10.1.2. Lyoc:

Lyoc is a technique that developed on the basis of the lyophilization. This process forms a porous and solid galenic form upon on lyophilization from an oil-in-water emulsion of active ingredient with excipients placed directly in the blister

packets. This technique was applied to the preparation of ODTs of poorly soluble drugs. By this process high dose of drug can be loaded into the preparations. The disadvantage of this process is the formed product possesses poor mechanical strength.

1.10.1.3. Quicksolv:

Quicksolv is a porous solid form obtained by freezing an aqueous dispersion/solution of the drug containing matrix and then drying it by removing the water using excess of alcohol (solvent extraction). The maximum drug loading capacity for water insoluble and soluble drugs are 400 mg and 60 mg, respectively. The primary problems associated with water soluble drugs are the formation of eutectic mixtures resulting in freezing-point depression and the formation of a glassy solid on freezing which might collapse on drying due to loss of supporting structure during sublimation process.

Advantages:

1. Tablets produced by this technology have very low disintegration time.
2. Tablets produced by this technology have great mouthfeel.

Disadvantages:

- This technology is an expensive and time consuming process.
- The product obtained is poorly stable and fragile.
- The conventional packaging is unsuitable for the products formed by this technique.

1.10.2. Tablet Moulding:

Tablet moulding is an old method of preparation of tablets. The different tablet moulding techniques in use are explained below.

1.10.2.1. Compression Moulding Process:

The tablets that produced by this process are less compact than compressed tablets with porous structure. The porous structure leads to the quicker dissolution rates. The technique follows the procedure as depicted below:

- Moistening of powder blend with an organic solvent.
- The coherent mass obtained is going to prepare into tablet by using mould plates.
- The organic solvent is then removed by air drying process.

1.10.2.2. Heat-Moulding Process:

This process leads to formation of molten mass containing a dispersed drug. This process uses agar solution as a binder. The blister packaging is suitable for tablets produced by this process. The technique follows the procedure as depicted below:

1. Preparation of a suspension contains drug, agar and sugar.
2. Pouring the suspension into the blister packages.
3. Solidifying the agar solution at 25°C to form a jelly.
4. Drying the jelly at 30°C under vacuum to form tablet.

1.10.2.3. Moulding by Vacuum Evaporation without Lyophilization:

This process involves pouring of the drug excipient mixture (in the form of a slurry or paste) into a mould of desired dimension, freezing the mixture to form a solidified matrix and finally subjecting it to vacuum drying at a temperature within the range of its collapse temperature and equilibrium freezing temperature.

Advantages:

Improving taste and mouthfeel.

rapid disintegration

Disadvantages:

Poor mechanical strength, they may undergo erosion and breaking during handling.

1.10.3. Direct Compression (DC):

Direct compression is a well known and simplest manufacturing technique for ODTs. It is most cost effective technique for the manufacturing of tablets. It is mostly using method because of its exclusive features like adoptability of the ordinary conventional manufacturing and packaging machinery.

1.10.3.1. Disintegrants:

In many ODT products based on direct compression process, the disintegrants mainly affect the rate of disintegration and hence dissolution which is further enhanced in the presence of water soluble excipients and effervescent agents. Tablet disintegration time can be optimized by focusing on the disintegrant concentration. Below a critical disintegrant concentration, tablet disintegration time becomes inversely proportional to disintegrant concentration. However, above the critical concentration level of disintegrant, disintegration time remains approximately constant or the decrease is insignificant.

1.10.3.1.1. Flashtab:

Flashtab is a technology designed based on the direct compression method. This technology produces coated crystals of drug and micro granules along with the disintegrants.

1.10.3.2. Effervescent Agents:

The formation of CO_2 from the effervescence agents made basis for utilization of this in the preparation of ODTs. The saliva in mouth causes the production of effervescence, which causes the tablet disintegration in mouth. Orasolv and Durasolv are the patented technologies prepared on this basis.

1.10.3.2.1. Orasolv:

Orasolv is the first-generation technology developed on the basis of effervescence to produce ODTs. The technique follows the procedure as depicted below:

1.Formulation of microparticles containing the drug with suitable polymer along with other excipients .

2.The formulated particles were dried at 50°C for one hour.

3.The dried particles sieved through 8 - mesh and dried for 1hour at 60°C.

4.Compression of dried microparticles into tablets at 1.0–2.0 kilo pound hardness.

1.10.3.2.2. Durasolv:

Durasolv, a second generation technology developed based on effervescence approach to produce ODTs. The tablets produced by this technique can give much faster release and cost effective. The product is suitable for the traditional blisterpacks or vials. The demerits of this technology are low drug loading capacity and high compaction pressure**.**

1.10.3.3. Sugar-Based Excipients:

This is another approach to manufacture ODTs by Direct compression technique. In this approach the sugar-based excipients (e.g., dextrose, fructose,

isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) were used to enhance the solubility and sweetness of the product. Thus the product formed will produce a good mouthfeel effect. Two types of saccharides are using in this technique those are as follows:

1)Type I saccharides (e.g., lactose and mannitol) exhibits low mouldability but high dissolution rate.

2)Type II saccharides (e.g., maltose and maltitol) exhibits high mouldability but low dissolution rate.

The mouldability of Type I saccharide can be enhanced by granulating it with a Type II saccharide solution.

1.10.3.3.1. Wowtab:

WOWTAB is a technology, which involves the use of fluidized bed granulation for the surface treatment of Type I saccharide with Type II saccharide. The WOWTAB formulation products are more stable than the Zydis or Orasolv products and suitable for both conventional bottle and blister packaging.

1.10.3.3.2. Ziplet:

Recently, the Ziplet technology is a newer technology developed recently, which can be used for hydrophobic drugs. The incorporation of water-insoluble inorganic excipient with one or more effective disintegrants gives an excellent disintegration.

1.10.4. Cotton Candy Process or Flashdose:

The FLASHDOSE is type of ODT manufactured by means of Shearform™ technology in association with Ceform TI™ technology to abolish the bitter taste of the medicament.

1.10.5. Spray-Drying:

For the making of ODTs the spray drying technique was used first by Allen. The formulation that he developed consisting of gelatin as a supporting agent (for matrix of tablet). Mannitol used as a bulking agent and sodium starch glycolate/croscarmellose as a disintegrant. The suspension of these above said

excipients was spray-dried to yield a porous powder. Then the porous powder was compressed into tablets.

1.10.6. Sublimation:

It is also a well acknowledged method for the preparation of ODTs. The ODTs produced by this method is very high porous. A porous matrix will form by sublimation of the volatile ingredients in the tablet.The volatile substances used in this process are ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethane. Cyclohexane and benzene were used as solvents.

The process involves formation of a tablet with the blend of volatile substances and subsequent removal of the solvent by sublimation. While sublimation the removed place of the volatile substance will stay unfilled and provide extremely porous structure which, leads to quick entry of saliva in the mouth and rapid disintegration of tablet. The tablets prepared by this technique are mechanically less stable.

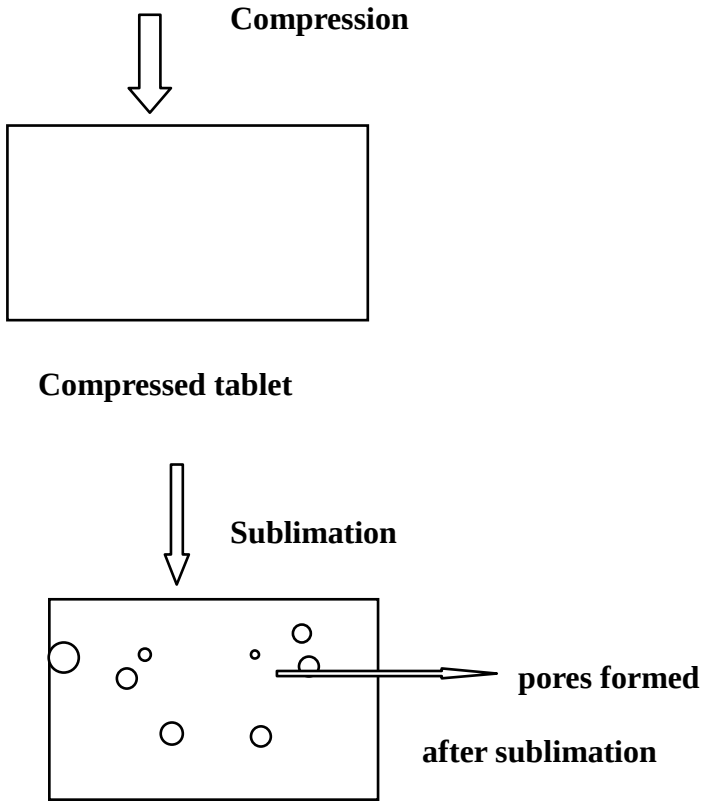


Figure:1.3: Sublimation technique

1.10.7. Mass-Extrusion:

The mass-extrusion technique is used for the preparation of ODTs mainly of bitter drugs due to its high taste masking property. The process is as follows:

The preparation of a soft blend of active constituent by incorporation of mixture of water soluble polyethylene glycol and methanol.Expulsion of above softened mass through an extruder or syringe to get a cylindrical shaped extrude.Formation of tablets by cutting extrude into even segments using heated blade

1.10.8. Nanonization:

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique.

The processes are depicted as flowcharts in Figure 1.4 A and 1.4 B.

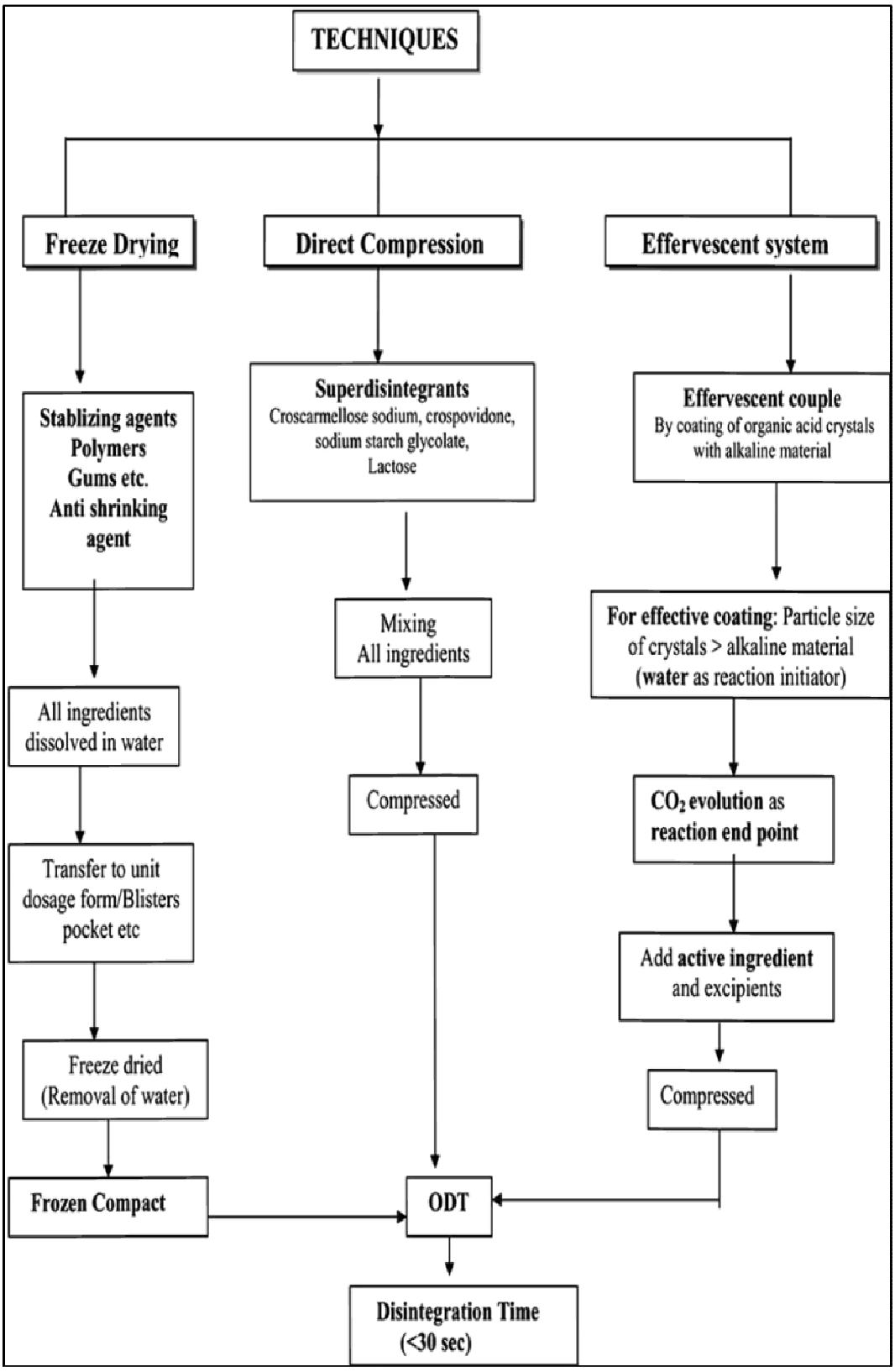


Figure 1.4 Processes Involved in the Preparation of ODTs

Table 1.2 List of Patented Technologies Based Branded Products

Patented Technology	**Basis of Technology**	**Technology Developed by Company**	**Active Ingredient (Brand Names)**
Zydis	Lyophilization	R.P.Scherer Inc.	Loratidine (Claritin Reditab and Dimetab)
Quicksolv	Lyophilization	Janssen pharmaceutics	Cisapride monohydrate (Propulsid (Quicksolv)
Lyoc	Lyophilization	Farmalyoc	Phloroglucinol Hydrate (Spasfon Lyoc)
Flashtab	Direct Compression	Ethypharm	Ibuprofen (Nurofen Flashtab)
Orasolv	Direct Compression	Cima Labs Inc.	Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt)
Durasolv	Direct Compression	Cima Labs Inc.	Hyoscyamine Sulfate (NuLev) Zolmitriptan (Zolmig ZMT)
Wowtab	Direct compression	Yamanouchi Pharma Tech.	Famotidine (Gaster D)
Ziplets	Direct compression	Eurand International	Ibuprofen (Cibalgina DueFast)

1.11.TABLET DISINTEGRATION AND DISINTEGRANTS:*(Debjit Bhowmik et al., 2009)*

Disintegration is the process of breaking up to smaller particles. Tablet disintegration is "the process of breaking up of tablet to the fine particles/ smaller pieces". A disintegrant helps the tablet to break up into smaller pieces upon contact with aqueous solution.

Disintegration of ODTs starts when a small amount of saliva contacts the dosage form (wetting) and penetrates the tablet matrix. Disintegrants or superdisintegrants with efficient disintegrating properties can be used in the formulation of ODTs. They are generally added at a level of 1 – 10% (w/w %).

The general mechanism of disintegration is shown in Figure 1.5.

1.11.1. Conceptual Diagram of Tablet Disintegration:

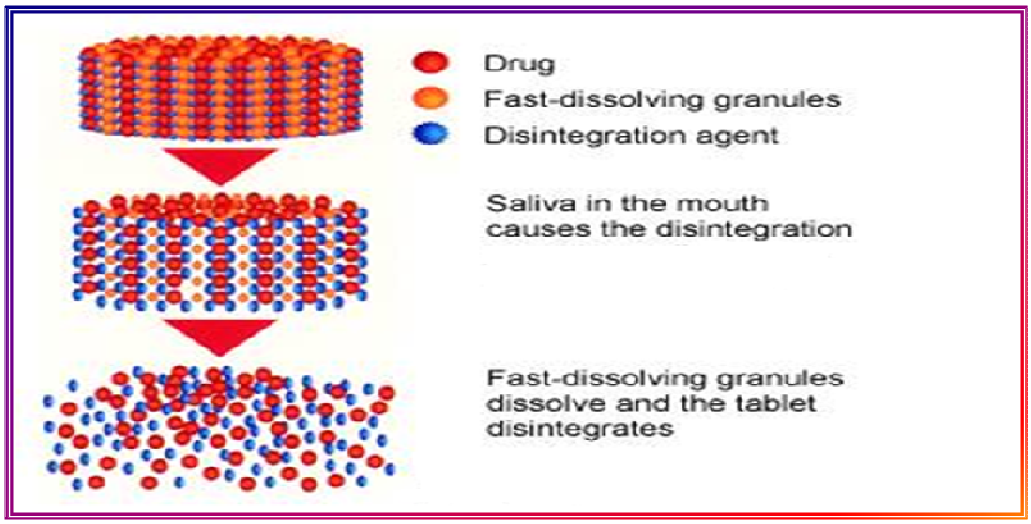


Figure 1.5 Mechanism of ODTs Disintegration

➢ There are four major mechanisms for tablets disintegration as follows,

1.11.1.1. Swelling:

It is the general mechanism of action for tablet disintegration. The porosity is main parameter to exert this action. The mechanism of disintegration is depicted in the Figure 1.6. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

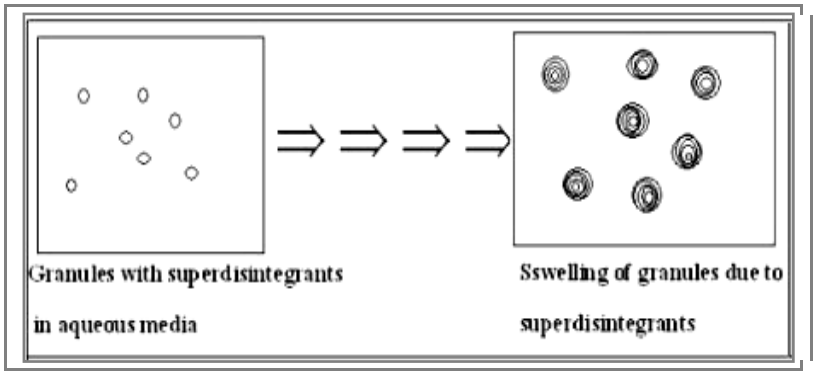


Figure 1.6 Disintegration Due to swelling

1.11.1.2. Porosity and Capillary Action (Wicking):

The mechanism of wicking is when a tablet contact with the medium the medium is pulled in to the tablet pores and causes to break the particulate forces inside that which intern leads to disintegration. It is given in Figure 1.7.

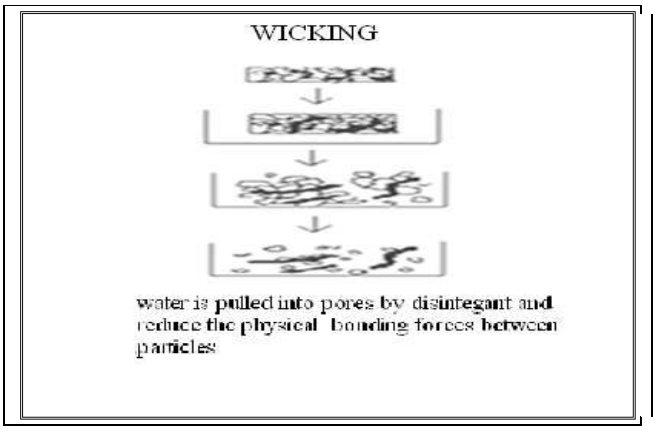


Figure 1.7 Disintegration Due to Wicking

1.11.1.3. Due to Disintegrating Particle/Particle Repulsive Forces:

It is followed by the 'non-swellable' disintegrants. The electric repulsive forces between particles lead to disintegration of ODTs. It is shown in Figure 1.8.

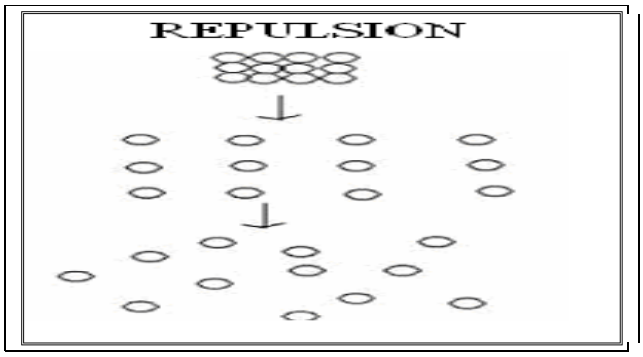


Figure 1.8 Disintegration Due to Repulsion

1.11.1.4. Due to Deformation:

As we know the deformation occurs in the tablet compression this deformation may fail when contact with medium. The second deformation that occurs in the above process or gaining of the original nature of components called as deformation here. The deformation process is given in Figure 1.9.

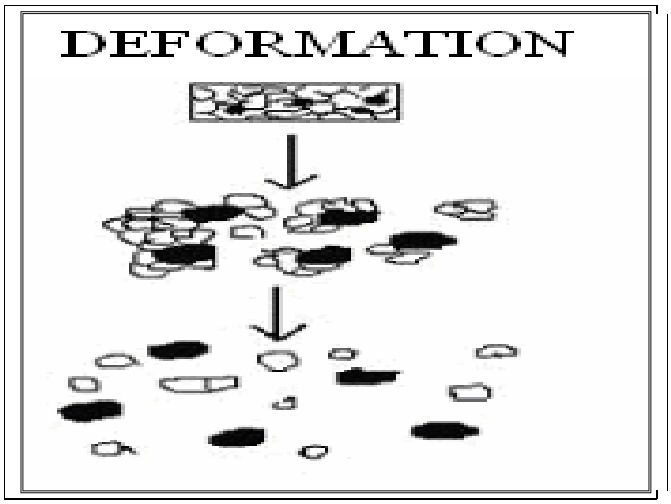


Figure 1.9 Disintegration Due to Deformation

1.11.2. Commonly used Superdisintegrants: (*Debjit Bhowmik et al., 2009)*

Table 1.3 List of Commonly Employed Superdisintegrants in ODTs

Superdisintegrants	Nature	Particle Size	Mechanism
Crospovidone	Cross linked homo polymer of N-vinyl-2-pyrrolidone	Particle size-100µm	Both swelling and wicking
Croscarmellose sodium	Cross-linked form of sodium CMC	Particle size 200 mesh	Swelling
Sodium starch Glycolate	Cross linked low substituted carboxy methyl ether of poly-glucopyranose	Particle size 140 mesh	Water uptake followed by rapid and enormous swelling
Acrylic acid derivatives	Poly(acrylic acid) super porous hydro gel	Insoluble in organic solvents, disperses in cold water	Wicking action
Effervescent mixture	Citric acid, tartaric acid, sodium bicarbonate	Crystalline nature	Effervescence
Sodium alginate	Sodium salt of alginic acid	Slowly soluble in water, hygroscopic	Swelling
NS-300	Carboxy methyl cellulose (CMC)	Particle size 106 µm	Wicking type
ECG-505	Calcium salt of CMC	Particle size 106µm	Swelling type
L-HPC	Low hydroxyl propyl cellulose	Particle size 106µm	Both swelling and wicking

Table 1.4 List of ODT Products Available in the Indian Market

Brand Name	Active Ingredient	Company
Domray MD	Domperidone	Ray remedies
Veirid MD	Domperidone	Shreyam healthcare
Omidon MD	Domperidone	Olcare labs
Zotacet MD	Cetrizine HCl	Zota pharma
Olanex Instab	Olanzepine	Ranbaxy
Romilast	Montelukast	Ranbaxy
Torrox MT	Rofecoxib	Torrent
Dolib MD	Rofecoxib	Panacea
Orthoref MD	Rofecoxib	Biochem
Zofex-25 MD	Rofecoxib	Zota pharma
Nexus MD	Nimesulide	Lexus
Nimex MD	Nimesulide	Mexon healthcare
Nisure-MD	Nimesulide	Suzen pharma
Olnim- MD	Nimuesulide	Olcare Lab

Table 1.5 List of ODT Products Available in the International Market

Brand Name	Active Ingredient	Company
Felden fast melt	Piroxicam	Pfizer Inc., USA.
Claritin redi Tab	Loratidine	ScheringploughCorp,USA.
Zyprexia	Olanzapine	Ei lily, USA.
Zofran ODT	Ondansetron	Glaxo Wellcome, UK.
Pepcid RPD	Famotidine	Merck and Co., USA.
Zoming- ZMT	Zolmitriptan	Astra Zeneca, USA.
Febrectol	Paracetamol	Prographarm, France.
Nimulid MDT	Nimusilide	Pancea Biotech, India.
Risperdal M Tab	Risperidone	Janseen pharmaceuticals
Tempra Quicklets	Paracetamol	Cima Labs, France.
Zolming Rapimelt	Zolmitriptan	Cima Labs, France.
Kemstro	Baclofen	Schwarz Pharma
Benadryl Fastmelt	Diphenhydramine	Pfizer Inc., USA.
Gaaster D	Famotidine	Yamanouchi.
Nasea OD	Ramosetron	Yamanouchi.

1.12. Salient Features of Mouth Dissolving Drug Delivery System

1) Ease of administration to pediatric, geriatric and psychiatric patients who refuse to swallow a tablet.

2) Convenient for administration and accurate dosing as compared to liquids.

3) No need of water to swallow the dosage form, which is highly convenient feature for patients who are depressed.
4) Good mouth feel property of MDDDS helps to change the basic impression of medication as 'Bitter Pill' particularly for pediatric patients.
5) As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.
6) Rapid dissolution and absorption of drug, which may produce rapid onset of action.
7) Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach, which enhances bioavailability of drugs by avoiding hepatic metabolism.
8) Ability to provide advantage of liquid medication in the form of solid preparation.

1.13. Strategies of Taste Masking: *(Roop K.Khar, 2001)*

a)Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Four fundamental sensations of taste have been described:

b)Sweet and salty, mainly at the tip.

c)Sour, at the sides.

d)Bitter, at the back.

e)Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist.

Various techniques available for masking bitter taste of drugs include taste masking with ingredients such as flavors, sweeteners, and amino acids; taste masking by polymer coating; taste masking by conventional granulation; taste masking with ion-exchange resins; taste masking by spray congealing with lipids; taste masking by formation of inclusion complexes with cyclodextrins; taste masking by the freeze-drying process; taste masking by making multiple emulsions; and taste masking with gelatin, gelatinized starch, liposomes, lecithins or lecithin-like substances, surfactants, salts, or polymeric membranes.

1.13.1. Taste Masking with Flavors, Sweeteners, and Amino Acids

This technique is the foremost and the simplest approach for taste masking, especially in the case of pediatric formulations, chewable tablets, and liquid formulations. But this approach is not very successful for highly bitter and highly water soluble drugs. Artificial sweeteners and flavors are generally being used along with other taste-masking techniques to improve the efficiency of these techniques. Aspartame is used as a prominent sweetener in providing bitterness reduction. A very small concentration (0.8%) is effective in reducing the bitterness of 25% acetaminophen. Starch, lactose, and mannitol have also exhibited taste-masking properties of caffeine. Anticholesterolemic saponin-containing foods, beverages, and pharmaceuticals are supplemented with amino acids (such as glycine and alanine) and flavors for bitterness control.

1.13.2. Taste Masking with Lipophilic Vehicles:

Lipids:

Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents. Guaifenesin has improved taste when mixed with carnauba wax and magnesium aluminium silicate and then melt-granulated.

Lecithin and Lecithin-like Substances:

Formulations with a large excess of lecithin or lecithin-like substances are claimed to control bitter taste in pharmaceuticals. Magnesium aluminum silicate with soybean lecithin is used to mask the unpleasant taste of talampicillin Hydrochloride. The drug is dissolved in or dispersed into an organic solvent such as chloroform. Lecithin is added to the solution or dispersion of the drug with stirring to give a blend. The blend is mixed with powdery excipients (e.g., magnesium aluminate metasilicate, synthetic aluminum silicate, lactose, mannitol, etc.), dried and granulated to give a taste-masked composition.

1.13.3. Taste Masking by Coating with Hydrophilic Vehicles:

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste masking while still providing acceptable bioavailability. A specialized technique, i.e.,

micro emulsion technology, has been used for taste masking of powders, chewable tablets, and liquid suspensions.

1.13.4. Carbohydrates (Cellulose):

The taste of orally administered drugs can be masked by coating the drug with carbohydrates. Bitter solid drugs such as pinaverium bromide, a spasmolytic, has no bitter taste when formulated in an organoleptically acceptable manner by polymer coating with a mixture of cellulose or shellac and a second film forming polymer soluble at pH less than 5.

1.13.5. Taste Masking by Inclusion Complexation:

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent, i.e., the host molecule, forming a stable complex. The complexing agent is capable of masking the bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. This method is most suitable only for low dose drugs. Vander Waals forces are mainly involved in inclusion complexes. The suppression of bitter taste by cyclodextrin was in increasing order of alpha, gamma, and beta cyclodextrin. β-cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide obtained from starch.

1.13.6. Solid Dispersion System:

Solid dispersion have been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method. Solid dispersion is also called as co precipitates for those preparation obtained by solvent method. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking. The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate. Solid dispersions using insoluble matrices or bland matrices may be used to mask the bitter taste of drugs. Also using them as absorbents on various carriers may increase the stability of certain drugs.

1.13.7. Prodrugs:

A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent drug. The alkyloxyalkyl carbonates of the clarithromycin 2’ position have remarkably alleviated bitterness and improved bioavailability when administered orally.Tasteless/bitter le ss prodrugs of opioid analgesics and antagonists were formulated for improved buccal delivery. Tasteless prodrugs of nalbuphine Hydrochloride, naltrexone, naloxone, oxymorphone Hydrochloride, butorphanonol, and levallorphan were synthesized for buccal administration to improve bioavailability relative to that of oral dosing without the characteristic bitter taste.

1.13.8. Ion Exchange Resin:

Another popular approach in the development of taste masking is based on ion exchange resin. Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion exchange is reversible and stiochiometric with the displacement of one ionic species by another. Ion exchange resins can be classified into four major groups:

a)Strong acid cation-exchange resin.

b) Weak acid cation-exchange resin.

c) Strong base anion-exchange resin.

d) Weak base anion-exchange resin.

e) Strong acid cation resins (sulfonated styrene di vinyl bezene copolymer product) function throughout the entire pH range and can be used for masking the taste of basic drugs. Weak acid cation exchange resins function at pH values above 6.0. Similarly, strong base anion-exchange resins function throughout the entire pH range and can be used for masking the taste of acidic drugs, while the weak base anion exchange resins function well below pH 7.0 Synthetic ion exchange resin have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950.

1.13.9. Miscellaneous Taste-Masking Approaches:

a)By Effervescent Agent:

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have also been employed for use as taste-masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption. It comprises a chewing gum base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition (e.g., oral anesthetics such as benzocaine and spilanthol) and other nonactive materials, such as sweeteners, flavoring components, and fillers. Recently, effervescent tablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption.

b)Salt Preparation:

Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water-soluble ibuprofen salts in aqueous solution. The bitter taste of caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid, and tartaric acid. Magnesium aspirin tablets are rendered tasteless by preparing magnesium salts of aspirin. Penicillin prepared as N, N'-dibenzylethylene-diamine diacetate salts or N, N'-bis (deyhdroabiety) ethylenediamine salts is tasteless. Bitterness-reduced antitussive and expectorant compositions (tablets) of dihydrocodeine phosphate, DL-methylephedrine

Hydrochloride, and D-chlorpheniramine maleate contain magnesium salts, sweeteners, starch, and cellulose.

c)Freeze Drying Process:

This method is used to develop fast-dissolving oral technologies such as Zydis and Lyoc technology. Zydis is a tablet-shaped dosage form that spontaneously disintegrates in the mouth in seconds. This is due to the high porosity produced by the freeze drying process. The Zydis process requires the active ingredient to be dissolved or suspended in an aqueous solution of water soluble structure formers. The resultant mixture is then poured into the preformed blister pockets of a laminate film and freeze dried. The two most commonly used structural excipients are gelatin and mannitol, although other suitable excipients can be used (e.g., starches, gums, etc.). This process is ideally suited to low solubility drugs as these are more readily freeze dried. Taste is very important for this type of dosage form and it is possible to produce palatable formulations by using artificial sweeteners (e.g., aspartame) and conventional flavors. Various drugs have been taste-masked by Zydis technology. These are lorazepam (Wyeth), piroxicam (Pfizer), loperamide (Janssen), ondansetron (Glaxo Wellcome), rizatriptan (Merck), loratadine (Schering Plough), olanzapine (Eli Lilly), selegiline (Elan), scopolamine/ chlorpheniramine (Taisho), etc.

1.14. TASTE ASSESSMENT:

Taste assessment one of the important quality control parameters for evaluation of taste masked formulation .Drug or formulation can be assessed using in vivo and in vitro method of taste evaluation parameters.

a)In vitro approaches taste assessment:

b)In vitro drug release studies:

Pharmacopoeial release studies have been modified by altering the chemical composition of the dissolution media (e.g. artificial saliva) and reducing the size of the basket screen size (screen size< 0.381 mm square opening) to prevent particles forms escaping. Taste masking is achieved when, in the early time points from 0-5 minutes the drugs substances in the dissolution medium is either not detected or amount is below the threshold for identifying its taste. Drug can be analyzed either spectrophotometrically or using HPLC. Of these HPLC is generally preferred especially when testing is performed in the presences of UV-absorbing component, such as flavorings and sweetener. A novel invivo buckle dissolution testing apparatus and method for the assessment of taste masking in oral dosages forms have recently been invented. The apparatus consists of a single, stirred, flow-through filtration cell including a dip tube designed to remove fine solid particles. Simulated saliva is used as the dissolution medium. The filtrated solution is removed from the apparatus continuously and used to analyze the dissolve drug.

1) Voltramettric electronic tongue:

The Voltramettric electronic tongue developed by s-*sense consistent of four working metal electrode made of gold, platinum, iridium and rhodium an Ag/AgCl references and a stainless steel counter electrode. A relay box enables the working electrode to be connected consecutively, to form four standards three-electrode configurations. The potentially pulse are applied by a potentiostat which is controlled

by a personnel computer. The PC used to set and control the pulse, measure and store current response, and to operate the relay box.

2)Electronic tongue:

The electronic tongue initially developed by the University of Taxes consists of a light sources, a sensors array and detector. The light sources shines onto chemically adapted polymer beads arranged on a small silicon wafer, which is known as a sensors chip the beads change is color on the basis of the presences and quality of specific chemical. The change is color is capture by a digital camera and the resulting signal converted into data using video capture board and a computer.

c) In vivo approaches for taste assessment

In vivo studies, stimuli are applied on to the tongue of either human or animals.

1) Human taste panel studies:

Human taste panel studies evaluated tastant (food, chemical, drug and so on) by estimating the gustatory sensation response in healthy human volunteers within well-controlled process. Such studies are there for also known as physiological evaluation, gustatory sensation testes or taste trials. They are sensitively measured of taste and are spastically designed to minimize bias and response within and between human volunteers. Well-established methodology for performing sensory analysis can be broadly divided into five types, namely discrimination taste. Scaling taste, experts testers, affective taste and descriptive methods and have been excellency discussed. Volunteers asses the taste quality and intensity of standard are taste stimuli on

different adjective scales including various properties of the sample, such as overall intensity, sweet, odor, bitter, metallic, cooling, hot, spicy, anesthetic, astringent etc. Each adjective can be rated as intensity rated on the scale zero to four a perhaps even up to nine points on the provided score rates.

2) Animal preference testes:

Bottle performance and condition taste aversion taste are used for taste for determining taste preference and concentration-response properties of tastant by animal 3 and 4 rats, mice, cats and dogs can be used for the potentiometrically e-tongue, incorporating and array of artificial lipid-polymer membranes as a fingerprint devices, has been developed as a promising tool for use in the quality control of phytomedicines. The miniaturization of taste sensors is particularly interest for the food and pharmaceutical industries. A portable low-cost sensing system has been made that interfaces to a Voltramettric electronic tongue sensors. Screen-printing technologies have been used to develop disposable taste sensors.

1.14. Patient Counseling in effective use of Fast Dissolving Tablets

ODT developed offers significant advantages for various groups of patients, but the majority of patients receiving ODT have little understanding of this novel dosage form. Patients receiving ODT may be surprised when tablets begin to disintegrate/dissolve in mouth. As pharmacists are ideal persons to know about the recent technologies, thus have opportunity to educate the patient for effective treatment. Counseling of patients about this dosage form can avoid any confusion and misunderstanding in taking ODT. Patient information that needs to be provided includes

1. Storage of this dosage form as some of ODT developed may not have sufficient mechanical strength, which needs to be handled carefully.
2. Patients with Siogren's syndrome or dryness of mouth or who take anti cholinergic drugs may not be suitable candidates for administering ODT. Although no water is required to allow drug to disperse quickly and efficiently but decreased volume of saliva may slow the rate of disintegration/dissolution and may reduce the bioavailability of the product
3. Patients need to be clearly told about the difference between effervescent and ODT. Some of technologies use effervescence, which experience a pleasing tingling effect on the tongue.
4. Although chewable tablets are available in market and patient need to be counseled about differences between chewable and ODT tablets. This ODT can be used easily in children who have lost their primary teeth and in geriatric patients who have lost their teeth permanently.
5. Patients may mistake fast-dissolving/disintegrating for effervescent tablets. Pharmacists may wish to stress the difference between the use of quick-dissolving and effervescent tablets. The Cima technologies, OraSolv and DuraSolv, use slight effervescence. Patients may experience a pleasant tingling on the tongue with OraSolv and DuraSolv.
6. With the pharmacists counseling, intervention and assistance about ODT, all patients receiving this novel dosage form could be more properly and effectively treated with greater convience.

NEED AND OBJECTIVES

2.NEED AND OBJECTIVES

The present study was expected to develop Losartan potassium taste masked porous tablets by sublimation technique by using sublimating agents.

In order to assist patients during travelling (where there will be unavailability of water), and to the patients who feel difficulty in swallowing, there is a necessity for the development of these oral disintegrating drug delivery systems. Losartan pottasium was rapidly absorbed and had less bioavailability, thereby an increased in the bio- availability of the drug may be observed if given as Losartan pottasium porous tablets.

The dosage form was designed in such a way that they disintegrate in patient's mouth upon on contact with saliva within seconds without aid of water. The drug then enters in to stomach as fine particles which may get rapidly absorbed and the pre gastric absorption leads to the faster onset of action. The investigation was undertaken with a view to formulate porous tablets and to get the quick onset of action in treatment of a suddenly arising hypertension. Use of sensory approach to enhance patient compliance and to evaluate these formulations by *in-vitro* methods and to select the best formulation among them in all dosage forms.

PLAN OF WORK

3.PLAN OF WORK

The study was planned to carry out as follows,

9) **LITERATURE SURVEY**

10) **FORMULATION AND DESIGN FOR POROUS TABLETS**

11) **PROCUREMENT OF DRUG AND EXCIPIENTS**

12) **EXPERIMENTAL WORK**

PRELIMINARY STUDIES

I) Identification of drug

a.By FTIR Spectroscopy

b.By Melting point

Physico-Chemical parameters

a.Organoleptic properties

b.Solubility profile

II) Analytical methods

a) Determination of λ_{max}

b) Development of standard curve of drug in the determined λ_{max}

c) Determination of percentage purity of drug

III) Determination of compatibility of drug with excipients

- By FTIR Spectroscopy
- By DSC Thermal Analysis

IV) Preparation and characterization of powder blend of porous tablets

- Angle of Repose
- Loose Bulk Density
- Tapped Bulk Density

- Hausner's Ratio
- Carr's Compressibility Index

V) Formulation

VI) Evaluation

7. General Appearance
8. Thickness and Diameter
9. Weight Variation
10. Hardness
11. Friability
12. Assay
13. Content Uniformity
14. *In-Vitro* Disintegration Time
15. Simulated Wetting Time
10. *In-Vitro* Dissolution Study

VII) Kinetics of *In-Vitro* drug release of porous tablets

VIII) Stability testing of selected formulation of porous tablets

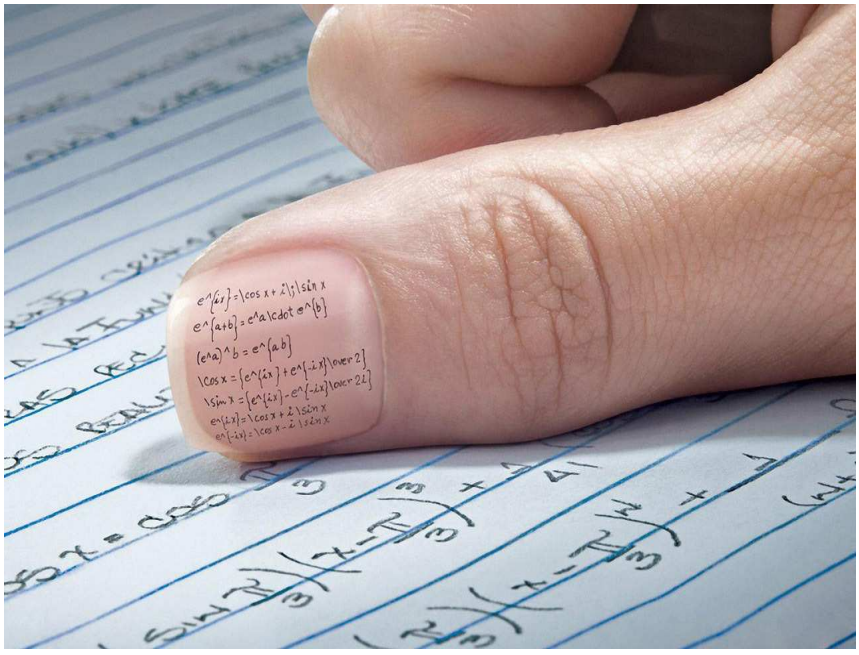
13) RESULTS AND DISCUSSION

14) SUMMARY AND CONCLUSION

15) FUTURE PROSPECTS

LITERATURE

SURVEY



4. LITERATURE REVIEW

Arun Arya, *et al*., (2010) published a review article deals with the history of the OTFs and a brief note on the OTF characteristic features including their advantages, composition, manufacturing methods, evaluating parameters. The article contains a new method for determination of dissolution rate called as conductivity method.

Basani Gavaskar D.M., *et al*., (2010) aimed to compact the sources of OTFs to give a collective overview on the Oral Fast Dissolving Films in this work. The article consists of the general information like advantages and disadvantages, formulation, evaluation and marketed preparations of Oral Films.

Brahmeswar Mishra, et *al*., (2009) wrote an overview on the Mouth Dissolving Drug Delivery systems. They primarily focused on the different formulation techniques and technologies that are using in the preparation of the Mouth Dissolving Drug Delivery systems. The article described very elaborately about each and every technology in a descriptive manner. They also included the patented technologies information that are using in the preparation of Oral Disintegrating Tablets. The article covers also the introduction about the Fast Dissolving Films.

Chaudhari P.D., *et al*., (2007) made Levocetrizine orodispersible tablet by preparing their complexes. The complex of the drug made with the ion exchange resin, Tulsion 335 (polyacrylic hydrogen with carboxylic functionality). Then the complex was formulated in to the orodispersible dosage form. The tablets were evaluated for various parameters like drug content, content uniformity, weight variation, hardness, friability, water absorption ratio, *in-vitro*, *in-vivo* disintegration time and *in-vitro* drug release. They found that the formulation containing the Tulsion was satisfactory for the taste mask and the results shown better disintegration and dissolution.

Debjit Bhowmik, *et al*., (2009) presented a comprehensive review on the Fast Dissolving Tablets which covers the ideal characteristics, limitations, manufacturing technologies, evaluation tests. The article also gives data about the mechanism of the tablet disintegration and list of the Fast Dissolving Tablets available in the market. It consists of list of superdisintegrants that can be used in the preparation of Fast Dissolving Tablets.

Devi V.K., *et al*., (2006) prepared orodispersible tablets of Fluconazole with two different ingredients that are ammonium chloride and camphor (volatalizable compounds). Eight formulations were prepared with varying concentrations of these two ingredients. They used the wet granulation technique. These tablets were evaluated for different tests like friability, weight variation, hardness, disintegration time and pH of the solution after dispersion. They reported the best formulation by comparing the prepared tablets with each other and finally with the marketed conventional tablets.

Gattani S.G., *et al*., (2009) developed Ondansetron mouth dissolving tablets. The approach selected for the rapid dissolving is superdisintegrant addition method. The superdisintegrants used in their study are Sodium starch glycolate, croscarmellose sodium and treated agar. The formulations containing superdisintegrants are compared with the blank formulation that does not contain the any superdisintegrant. The prepared formulations are checked for different evolutionary parameters and finally concluded that croscarmellose sodium is best disintegrant.

Gohel M.C., *et al*., (2007) fabricated Valdecoxib oral films using different film forming polymers like Eudragit EPO and hydroxyl propyl methyl cellulose and in their combinations. The oral films were prepared by the film casting method. They used the glycerol; menthol and aspartame in their formulation as plasticizer, cooling

agent and sweetener. The films were cutted in to a convenient size in the size of 4 cm^2 area. The films were evaluated for different parameters like hydration study, folding endurance and *in-vitro* drug dissolution (in the distilled water) for optimization. They observed that the films containing the higher concentration of glycerol showed higher water uptake and faster drug release.

Jae Han Park., *et al*., (2008) developed a method for the determination of the Disintegration time of the Oral Disintegrating Tablets. The method is useful in the place of USP disintegration test. It is a simple method can develop in lab scale. They used 22 mm diameter polystyrene microplate, Sensient blue dye and a Whatman filter paper for the test. The test is named as Simulated Wetting Time.

Karthikeyan D., *et al*., (2008) developed modified ocular inserts of Indomethacin for the prolonged action and better patient convenience and the solvent casting technique was used for their formulation. Eudragit RS 100 and Ethyl cellulose were used as polymers and dichloromethane and dibutyl phthalate were used as solvent and plasticizer respectively. The formulations were evaluated for different parameters like drug- excipient interaction, Physico-chemical characteristics and stability studies. The best formulation was showed zero order release pattern.

Kaushik D., *et al*., (2004) prepared the mouth dissolving tablets of Olanzapine drug. These selected effervescent formulation approach for the preparation. The effervescent excipient not only helps in faster disintegration but also masks the slight bitter taste of medicament. Sodium bicarbonate and citric acid were used as effervescent agents were selected in the work and their ratio in the formulation was optimized. The prepared formulations were evaluated for different parameters like hardness, disintegration, friability, dissolution etc., and best formulation was reported by using the disintegration time and dissolution behavior.

Mukesh Gohel., *et al.*, (2004) designed Nimesulide mouth dissolving tablets. They used vacuum drying technique in the preparation of the mouth dissolve tablets. The vacuum drying technique produces a porous structure that can be facilitating the dissolution so they chosen this approach. They prepared tablets by wet granulation technique and the granule blend contains the crospovidone as a superdisintegrants and the camphor as a subliming agent. The concentration of the crospovidone was optimized by application of the 3^2 factorial approaches. The ordinary tablets were prepared by the using a sufficient compression force and later these were made porous by sublimation technique at 60°C. The prepared tablets were evaluated for different parameters like hardness, friability, wetting time, drug content, water absorption ratio, *in- vitro* disintegration time and *in-vitro* drug release. Best formulation was finalized by the *in- vitro* drug release pattern. They concluded that vacuum drying can be used as an alternative method for the production of MDTs.

Na Zhao, *et al.*, (2005) were aimed to compare the disintegration efficiency and the development of a test model for the 3 classes of superdisintegrants what they were used in their present work. The 3 superdisintegrants used were as follows, Ac-Di-Sol, Primojel, and Polyplasdone XL. For the proto type formulation the 3 superdisintegrants were made in to tablets with the incorporation of a traditional drug Aspirin. For the examining the disintegration of each tablet these used a novel approach i.e. Using a digital video camera. From this data they analyzed the best superdisintegrant by different statistical approaches and they found the Ac-Di-Sol tablets rapidly disintegrating comparing to other superdisintegrants.

Nagendrakumar D., *et al.*, (2009) prepared the Fexofenadine HCl Fast dissolving tablets. These selected effervescent formulation approach for the preparation. The effervescent agents used were sodium bicarbonate and the citric acid. The

superdisintegrants used were crospovidone, croscarmellose sodium and sodium starch glycolate. Sodium bicarbonate and citric acid ratio in the formulation was optimized. The prepared formulations were evaluated for different parameters like hardness, friability, drug content uniformity and *in-vitro* dispersion time and finally the best formulation among the prepared were compared with the commercial conventional tablet formulation.

Panigahi Patel, *et al.*, (2005) produced an article which covers a review on the Mouth Dissolving Tablets. The article covers the ideal characteristics, limitations, manufacturing technologies, evaluation tests. They described about the oral absorption test and different dissolution medias used in the evaluation of the MDTs.

Rakesh Patel, *et al.*, (2009) formulated an Ondansetron edible film. The film forming polymers selected in this study were low viscosity grade hydroxypropyl methylcellulose (HPMC E 15) and Maltodextrin and in their combination. They selected these because of their excellent film forming property and palatable taste. Glycerol and carragenan were added for their plasticizing and stabilizing properties. The films prepared from the high concentration of maltodextrin leads to formation of a brittle film, when compared with the film formations containing the lower concentration. In the same way the higher concentration of HPMC E 15 was resulted in sticky film formation. The best formulation that they reported after the all quality checking tests was the formulation containing 25%w/w Maltodextrin and HPMC E 15 20%w/w.

Ravi Kumar, *et al.*, (2008) prepared Fast dissolving tablets of Captopril. These developed the tablets by two different approaches named as wow tab and effervescent technology. The excipients used in both the technologies not only aid fast disintegration of tablets, but also mask the slight bitter taste of drug. The sodium

bicarbonate and citric acid were used in the effervescent approach and the maltose and lactose were used in the wow tab technology. All the prepared formulations were evaluated for different quality control tests like thickness, friability, weight variation, drug content, and disintegration time and drug dissolution. Study has shown that 8:6 ratio of sodium bicarbonate and citric acid in the Captopril fast dissolving tablets gave good soothing and excellent mouth feel.

Renuka Mishra, *et al.*, (2009) prepared Cetrizine rapid disintegrating films. The classes of polymers that are fast disintegrating and having good film-forming properties (e.g., hydroxypropyl methylcellulose [HPMC], Pullulan, and hydroxypropyl cellulose [HPC]) were taken in the preparation of films. Various grades of HPMC E LV (i.e., E3, E5, and E15) were taken into consideration. Out of available methods such as solvent casting, semisolid casting, hot melt extrusion, solid dispersion extrusion, and rolling the solvent casting technique was selected in their study for preparation of the films due to their advantages like common and traditional method. The prepared films of Cetrizine were checked for the tests like thickness, mechanical properties such as tensile strength and elasticity, *in-vitro* and *in-vivo* disintegration, and *in-vitro* dissolution. Out of the different grades of polymers that they selected the HPMC E 3LV was reported as most suitable polymer.

Shastry C.S., *et al*., (2004) focused on different taste masking techniques because the taste is an important parameter in developing the oral dosage forms. The article describes different taste masking approaches that are using in the present pharmaceutical industries and list of some therapeutic agents that have bitter taste. The simple and cost efficient method out of these is sensory approach.

Shirsand S.B., *et al.*, (2010) designed a fast disintegrating tablet formulation of Prochlorperaziine by incorporation of disintegrants. They selected croscarmellose

sodium, crospovidone, and sodium starch glycolate as superdisintegrants and direct compression technique for preparing the tablets.

Sumitha Ch., *et al.*, (2009) prepared rapid disintegrating films (RDFs) of Ondansetron HCl to improve the patient convenience. The methocel E15 polymer was used as film forming polymer. The Ondansetron HCl was bitter drug so it was formulated as complexion with the ion exchange resin Polacriline Potassium. The Polacriline Potassium had disintegrating property. For more taste masking and patient convenient the authors used sweetener and flavors. For the flavoring instead of the single flavor three different flavors viz., vanilla, lychee and banana. The prepared formulations were evaluated for different quality tests. The formulation which does not release the drug in the saliva was selected for the best formulation. The formulation also shows the rapid release of the drug due to disintegration of the polymer methocel E15.

Suresh Bandari, *et al.*, (2008) presented a comprehensive review on the Oral Disintegrating Tablets. The review covers definition of ODTs, challenges in development, the ideal characteristics, limitations, manufacturing technologies, evaluation tests. The article also gives data about the mechanism of the tablet disintegration and list of the Oral Disintegration Tablets available in the Indian and International market. The article describes the various disintegration methods for evaluation of Oral Disintegration Tablets like rotator shaft method, sieve method.

Suvakanta Dash, *et al.*, (2009) wrote a review article on the release kinetics of the controlled drug delivery systems. The article gives information about the zero order release, first order release kinetic modeling with equations.

Literature review indicating work carried out on selected drug, Losartan potassium is given below:

Sasidhar R.L.C, et al. (2010) In the present investigation an attempt has been made to increase therapeutic efficacy, reduced frequency of administration and improved patient compliance by developing controlled release matrix tablets of Losartan Potassium. Losartan Potassium was formulated as oral controlled release matrix tablets by using poly (ethylene oxides) {Polyox WSR 303}.The aim of this study was to investigate the influence of polymer level and type if fillers namely lactose [soluble filler], microcrystalline cellulose and anhydrous dibasic calcium phosphate [insoluble fillers] on the release rate and mechanism of Losartan Potassium from matrix tablets.

Rout Prasant kumar, *et al*. (2009) Present investigation describes preparation of microspheres prepared by solvent evaporation method followed by *invitro* characterization statistically. Microspheres containing Losartan potassium were prepared by solvent evaporation method by using ethyl cellulose and Acycoat L30D as rate controlling polymer. The microspheres were found to be discrete, spherical with free flowing properties. The morphology (Scanning Electron Microscopy), particle size distribution, total entrapment of Losartan potassium into the microparticles and their release profiles were investigated.

Reena T, *et al*. (2009) The purpose of the current study was to investigate the feasibility of proniosomes as transdermal drug delivery system for losartan potassium. Different preparations of proniosomes were fabricated using different nonionic surfactants, such as Span 20, Span 40, Span 60, Span 80, Tween 20, Tween 40, and Tween 80. Different formulae were prepared and coded as PNG-1 (proniosomal gel-1) to PNG-7.

Chopra S, *et al.* (2006) The aim of the present research work was to systemically device a model of factors that would yield an optimized controlled release tablet dosage form of an anti-hypertensive agent, losartan potassium. Independent variables such as the amount of the release retardant polymers- Methocel K15M(X_1), Methocel K100M(X_2) and Sodium carboxy methyl cellulose(X_3) were optimized using a 3-Factor, 3-level Box-Behnken statistical design. The dependent variables selected were the burst release in 15min (Y_1), cumulative % release of losartan potassium after 60 min. (Y_2) and hardness (Y_3) of the tablets.

Shruti C, *et al.* (2006) The aim of the present research work was to systemically device a model of factors that would yield an optimized sustained release tablet dosage form of an anti-hypertensive agent, losartan potassium, using response surface methodology by employing a 3-Factor, 3-level Box-Behnken statistical design. Independent variables studied were the amount of the release retardant polymers- HPMC K15M(X_1), HPMC K100M(X_2) and Sodiumcarboxy methylcellulose(X_3). The dependent variables selected were the burst release in 15min.(Y_1), cumulative % release of losartan potassium after 60 min. (Y_2) and hardness(Y_3) of the tablets with constraints on the Y_2= 31-35%.

DRUG AND EXCIPIENTS PROFILE

5.DRUG AND EXCIPIENTS PROFILE

5.1. DRUG PROFILE

Losartan potassium *(IP, 2007; BP, 2009; Merck Index, 1997; USP, 2009; Clark's, 2004; KD Tripathi, 2008)*

Losartan potassium is an angiotensin II receptor (type AT_1) antagonist.

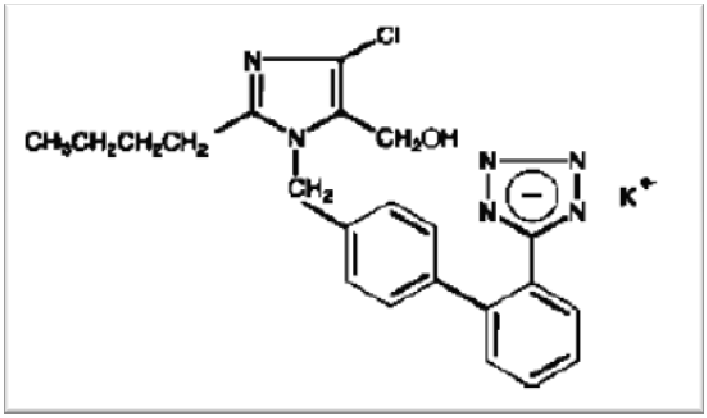
Proprietery Name: ACTILOP, LOSCOM , LOSACAR.

Molecular formula : $C_{22}H_{22}ClKN_6O$,

Molecular weight: 461.01 g/mole.

Chemical name: 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5ylphenyl)benzyl]imidazole-5- methanol monopotassium salt.

Structural formula :



Solubility: It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

Category: Anti hypertensive drug.

Dose: 25mg, 50mg.

Melting point: 183.5-184^{0}C.

P^{Ka} : 5-6.

Bioavailability : 33%.

Angiotensin –II receptor subtype1 antagonist.

Description: Losartan potassium is a white to off-white free-flowing crystalline powder. It is a non-peptide molecule. Oxidation of the 5 hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Storage: Store at 25°C 15-30°C Temperature]. Keep container tightly closed. Protect from light.

SIDE EFFECTS:

Many people using this medication do not have serious side effects.

Fainting, decreased sexual ability, change in the amount of urine, stomach/abdominal pain, severe nausea, yellowing eyes or skin, dark urine, unusual fatigue, muscle pain.

Symptoms of an allergic reaction include: rash, itching, swelling (especially of the face, lips, tongue, or throat), severe dizziness, trouble breathing.

Adverse events occurred at about the same rates in men and women, older and younger patients, and Black and non-Black patients.

Superficial peeling of palms and hemolysis were reported in one subject.

CLINICAL PHARMACOLOGY:

Mechanism of Action

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT_1 receptor. Neither losartan nor its active

metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin).

Pharmacokinetics

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P_{450} enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed.The terminal half-life of losartan is about 2

hours.The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Absorption:

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%.

Distribution:

Both losartan and its active metabolite are highly bound to plasma proteins i.e., 98% plasma protein bound, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses.

Elimination:

The terminal half-life of losartan is about 2 hours.

Pharmacodynamics and Clinical Effects

Adult Hypertension

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration.

In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

USES:

This drug is used to treat high blood pressure (hypertension) and to help protect the kidneys from damage due to diabetes. It is also used to lower the risk of strokes in patients with high blood pressure and an enlarged heart. High blood pressure reduction helps prevent strokes, heart attacks, and kidney problems. This drug works by blocking the hormone angiotensin thereby relaxing blood vessels, causing them to widen. Losartan belongs to a class of drugs called angiotensin receptor blockers.

OTHER USES:

This drug may also be used to treat congestive heart failure.

HOW TO USE: Take this medication by mouth, usually once daily or as directed by your doctor. You may take this drug with or without foodIt is important to continue taking this medication even if you feel well.

PRECAUTIONS:

Before taking losartan, tell your doctor or pharmacist if you are allergic to it; or to ACE inhibitors (e.g., captopril, lisinopril); or if you have any other allergiesespecially of: kidney disease, liver disease, high blood levels of potassium, heart problems, severe dehydration (and loss of electrolytes such as sodium).

This drug may make you dizzy; use caution engaging in activities requiring alertness such as driving or using machinery. Limit alcoholic beverages.

PREGNANCY CONTRAINDICATIONS

This medication is not recommended for use during pregnancy due to the risk for harm to an unborn baby. Breast-feeding is not recommended due to the potential harm to the nursing infant.

PATIENT INFORMATION:

Pregnancy:

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Potassium Supplements

A patient losartan potassium receiving should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

DRUG INTERACTIONS:

Digoxin, fluconazole, lithium, "water pills" (diuretics such as furosemide; potassium-sparing diuretics such as amiloride, spironolactone, triamterene), rifampin. As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics and potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. A patient with known hypersensitivity to aspirin and penicillin, when treated with losartan, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

MISSED DOSE:

If you miss a dose, use it as soon as you remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

- **Dosage Forms:**
- Tablet: Actilop: 25mg, 50mg.
- FC-Tablet : Losapot: 25mg, 50mg.

5.2. EXCIPIENTS PROFILE:

a)CAMPHOR (http://en.wikipedia.org/wiki/camphor)

Nonproprietory name: None adopted.

Synonyms: Camfora ,alcanfor, root bark oil.

Functional Category: Rubefacient,counter irritant.

Empirical Formula: $C_{10}H_{16}O$

Molecular Weight: 152.2

Brand name: Camphora synthetic tablets,camphora.

Description: White solid translucent crystals Fine .

odour : Aromatic.

Typical Properties:

Solubility: Soluble in ethanol,turpentine and essential oils..

Stability and storage conditions:

Not Stable , Store in a well closed container .

As it sublimes at room temperature.

Shelf life: five years

b)THYMOL (http://en.wikipedia.org/wiki/thymol)

Nonproprietary Names:B.P:Thymol, USPNF:Thymol, PhEur:Thymolum.

Synonyms: Acidotrimico;Flavinol,intrasol,isopropylcresol,isoproply metacresol,timol,m-thymol,thymic acid.

Chemical Name: Thymol

CAS Registry Number: [89-83-8]

Empirical Formula : $C_{10}H_{14}O$

Molecular Weight : 150.24

Functional Category : Antioxidant,antiseptic,disinfectant,flavouringagent,therapeutic agent,skin penetrant.

Applications in Pharmaceutical Formulation or Technology:

Thymol is a phenolic antiseptic,which has anyibacterial and antifungal activity.Thymol is more powerfull disinfectant than phenol,but its low water solubility,its irritancy to tissues,and its inactivation due to organic material,such as proteins,limits its use as disinfectant.Thymol is chiefly used as a deodrant in antiseptic.

Solubility: Soluble in ethanol,chloroform,ether,glacial acetic acid,essential oils ,fixed oils and fats.sparingly soluble in glycerin.

Incompatibilities: Thymol is incompatible with iodine,alkalis and oxidising agent.

Stability and storage: Thymol should be stored in well closed ,light resistant containers,in cool,dry place.Thymol is affected by light.

c)MENTHOL (Raymond C. Rowe, 2003)

Nonproprietary Names: B.P:Racementhol, USP:Menthol, PhEur:Mentholum racemicum.

Synonyms: Hexahydrothymol,peppermint camphor,racemic menthol,dl-menthol,3-p menthanol,p-menthan -3-ol.

Chemical Name: (1RS,2RS,5RS)-(Æ)-5-Methyl-2-(1-methylethyl)cyclohexanol

[15356-70-4] .

Empirical Formula : $C_{10}H_{20}O$

Molecular Weight : 156.27

Functional Category : Flavouring agent,therapeutic agent.

Applications in Pharmaceutical Formulation or Technology:

Menthol is widely used in pharmaceuticals, confectionery, and toiletry products as a flavoring agent or odour enhancer. In addition to its characteristic peppermint flavor, l-menthol, which occurs naturally, also exerts a cooling or refreshing sensation that is exploited in many topical preparations. Unlike mannitol, which exerts a similar effect due to a negative heat of solution, l-menthol interacts directly with the body's coldness receptors. d-Menthol has no cooling effect, while racemic menthol exerts an effect approximately half that of l-menthol. When used to flavor tablets, menthol is generally dissolved in ethanol (95%) and sprayed onto tablet granules and not used as a solid excipient.

Solubility: very soluble in ethanol (95%), chloroform, ether, fatty oils and liquid paraffin; soluble in acetone and benzene; very slightly soluble in glycerin; practically insoluble in water.

Incompatibilities: Incompatible with: butylchloral hydrate; camphor; chloral hydrate; chromium trioxide; b-naphthol; phenol; potassium permanganate; pyrogallol; resorcinol; and thymol.

Stability and storage: A formulation containing menthol 1% w/w in aqueous cream has been reported to be stable for up to 18 months when stored at room temperature.(1)

Menthol should be stored in a well-closed container at a temperature not exceeding 258C, since it sublimes readily.

d)AMMONIUMBICARBONATE(http://en.wikipediaorg/wiki/Ammonium_bicarbonate)

Nonproprietary Names: Ammonium bicarbonate.

Synonyms: Sal volatile, salt of hartshorn, baking soda, baking powder.

Synonyms: Bakers ammonia.

Chemical Name: Ammonium bicarbonate.

Functional Category : Leavening agent.

Applications in Pharmaceutical Formulation or Technology:

It is used as an emetic.As well as smelling agent,it is used as leavening agent till today, particularly in recipes.Ammonium bicarbonate is also found in smokeless tobacco products such as skoal. Buckleys cough syrup from canada uses ammonium bicarbonate as active ingredient which relieves bronchitis.

Solubility: Very soluble water and alcohol,bicarbonate is not soluble in alcohol.

Stability and storage: Store in well closed container as it sublimes easily.

e)CROSPOVIDONE: (Raymond C Rowe, 2003)

Nonproprietary Names

- BP: Crospovidone
- PhEur: Crospovidonum
- USPNF: Crospovidone

Synonyms : Crosslinked povidone, Kollidon CL, Kollidon CL-M, Polyplasdone XL, PolyplasdoneXL-10, polyvinylpolypyrrolidone.

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer

CAS Registry Number: [9003-39-8]

Functional Category: Tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity,with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets.7 Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Description: Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Typical Properties

Acidity/alkalinity: pH = 5.0–8.0 (1% w/v aqueous slurry)

Density: 1.22 g/cm3

Moisture content: Maximum moisture sorption is approximately 60%.

Solubility: Practically insoluble in water and most common organic solvents.

Stability and Storage Conditions: Crospovidone is hygroscopic; it should be stored in an airtight container in a cool, dry place.

Incompatibilities: Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some Materials.

f)MICROCRYSTALLINE CELLULOSE : (Raymond C. Rowe, 2003)

Nonproprietary Names:

BP: Microcrystalline cellulose

JP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

Synonyms: Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose;

E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Chemical Name: Cellulose

CAS Registry Number: [9004-34-6]

Molecular Weight: 36 000

Functional Category:

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Description:

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Typical Properties:

Density (bulk): 0.337 g/cm3;

Density (tapped): 0.478 g/cm3;

Density (true): 1.512–1.668 g/cm3

Flowability: 1.41 g/s

Melting point: chars at 260–270°C.

Specific surface area: 1.06–1.12 m2/g for Avicel PH-101;

1.21–1.30 m2/g for Avicel PH-102;

0.78–1.18 m2/g for Avicel PH-200.

1.21–1.30 m2/g for Avicel PH-102;

Moisture content: Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic. **(**Avicel PH- 102= ≤5.0)

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Applications in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and directcompression processes. Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Uses of microcrystalline cellulose

1.Adsorbent

2.Capsule binder/diluents

3.Tablet disintegrants

4.Tablet binder/diluents

Stability and Storage Conditions: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents.

g)MANNITOL (Raymond C. Rowe, 2003)

Nonproprietary Names

- BP: Mannitol
- JP: D-Mannitol
- PhEur: Mannitolum
- USP: Mannitol

Synonyms: Cordycepic acid, C*PharmMannidex, manna suga, D-mannite, Pearlitol.

Chemical Name: D-Mannitol

CAS Registry Number: [69-65-8]

Empirical Formula: C6H14O6 182.17

Functional Category: Diluent; diluent for lyophilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.

Applications in Pharmaceutical Formulation or Technology:

- Mannitol is widely used in pharmaceutical formulations and food products.
- In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet Formulations.

16) Mannitol may be used in direct-compression tablet applications.

In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. Mannitol has also been used to prevent thickening in aqueous antacid

suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations **Density (bulk):**

- 0.430 g/cm3 for powder;
- 0.7 g/cm3 for granules.

Density (tapped):

- 0.734 g/cm3 for powder;
- 0.8 g/cm3 for granules.

Density (true): 1.514 g/cm3

Melting point: 166–168°C.

Stability and Storage Conditions:

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions.

h)ASPARTAME : (Raymond C. Rowe, 2003)

Nonproprietary Names

- BP: Aspartame
- PhEur: Aspartamum

• USPNF: Aspartame

Synonyms

- 3-Amino-N-(α-carboxyphenethyl)succinamic acid N-methyl ester
- 3-amino-N-(α-methoxycarbonylphenethyl)succinamic acid
- Aspartyl phenylamine methyl ester;

Chemical Name: N-α-L-Aspartyl-L-phenylalanine 1-methyl ester.

CAS Registry Number: [22839-47-0]

Empirical Formula: $C_{14}H_{18}N_2O_5$

Functional Category: Sweetening agent.

Applications in Pharmaceutical Formulation or Technology:

3. Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets,powder mixes, and vitamin preparations.

4. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

5. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal). Therapeutically, aspartame has also been used in the treatment of sickle cell anemia

i)TALC: (Raymond C. Rowe, 2003)

Nonproprietary Names: BP Purified talc; IP Talc; PhEur Talcum; USP Talc.

Synonyms: Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc;purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical Name and CAS Registry Number: Talc [14807-96-6]

Empirical Formula and Molecular Weight: Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Functional Category: Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology: Talc was once widely used in oral solid dosage formulations as a lubricant and diluents.

Uses in Concentration (%)

- Dusting powder 90.0 to 99.0
- Glidant and tablet lubricant 1.0 to 10.0
- Tablet and capsule diluent 5.0 to 30.0

Although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricantin tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized

when used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Description: Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Typical Properties

Acidity/alkalinity: pH = 7 - 10 for a 20% w/v aqueous dispersion.

Hardness (Mohs): 1.0 - 1.5

Moisture content: Talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Particle size distribution: Pharmaceutical Excipients 2215 varies with the source and grade of material. Two typical grades are = 99% through a 74 μm (#200 mesh) or =°99% through a 44 μm (#325 mesh).

Solubility: Practically insoluble in dilute acids and alkalis, organic solvents and water.

Specific gravity: 2.7–2.8

Specific surface area: 2.41–2.42 m^2/g

Stability and Storage Conditions: Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. Talc should be stored in a well-closed container in a cool, dry place.

Related Substances: Bentonite; magnesium aluminum silicate; magnesium silicate; magnesium trisilicate.

Comments: Various different grades of talc are commercially available that vary in their chemical composition depending upon their source and method of preparation.

j)MAGNESIUM STEARATE (Raymond C. Rowe, 2003)

Nonproprietary Names :

1. BP: Magnesium stearate
2. JP: Magnesium stearate
3. PhEur: Magnesii stearas
4. USP: Magnesium stearate

Synonyms **:** Magnesium octadecanoate, stearic acid magnesium salt, octadecanoic acid, magnesium salt

Chemical Name **:** Octadecanoic acid magnesium salt

CAS Registry Number **:** 557-04-0

Empirical Formula **:** $C_{36}H_{70}MgO_4$

Molecular Weight **:** 591.34

Structural Formula **:** $[CH_3(CH_2)_{16}COO]_2Mg$

Functional Category **:** Tablet, capsule lubricant

Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate use was reported not only in the pharmaceuticals, but also in the cosmetics, and food products.

The major action of the Magnesium stearate is lubricant. In 0.25-5.0 percent concentration it acts as lubricant in capsule and tablet manufacturing.

The use of magnesium stearate in creams also reported.

Description: Magnesium stearate is a fine, white, precipitated or milled, impaltable powder. It haves low bulk density. It had a faint odor of stearic acid. The taste of magnesium stearate is characteristic. It is greasy to touch.

Handling Precautions: While handling the magnesium stearate eye protection and gloves are recommended.

MATERIALS AND EQUIPMENTS

6. MATERIALS AND EQUIPMENTS

Table 6.1 : List of Materials and their Suppliers

S. No.	Name of Raw Materials	Name of the Supplier
1.	Losartan potassium	Actavis Pharmaceuticals, Chennai.
2.	Camphor	Concept Pharmaceuticals, Aurangabad.
3.	Crospovidone	Concept Pharmaceuticals, Aurangabad.
4.	Thymol	Concept Pharmaceuticals, Aurangabad.
5.	Menthol	Qualigens Fine Chemicals, Mumbai.
6.	Ammonium Bicarbonate	Loba Chemie Pvt. Ltd., Mumbai.
7.	Mannitol	Loba Chemie Pvt. Ltd., Mumbai.
8.	Aspartame	GK Labs, Acharapakkam.
9.	Pineapple Flavor	GK Labs, Acharapakkam.
10.	Magnesium Stearate	Loba Chemie Pvt. Ltd., Mumbai.
11.	Microcrystalline Cellulose PH 102	Loba Chemie Pvt. Ltd., Mumbai.
12.	Talc	GK Labs, Acharapakkam.
13.	Hydrochloric Acid	Loba Chemie Pvt. Ltd., Mumbai.
14.	Methanol	Loba Chemie Pvt. Ltd., Mumbai.
15.	Acetone	Loba Chemie Pvt. Ltd., Mumbai.
16.	Ethanol	Qualigens Fine Chemicals, Mumbai.
17.	Sodium Hydroxide	Loba Chemie Pvt. Ltd., Mumbai.
18.	Potassium di Hydrogen Phosphate	Loba Chemie Pvt. Ltd., Mumbai.
19.	Sensient Blue	Qualigens Fine Chemicals, Mumbai

Table 6.2 : List of equipments used and manufacturers

S. No.	Name of Equipments	Company	Model
1.	Differential Scanning Calorimeter	Shimadzu, Japan.	DSC 60
2.	Digital pH Meter	Elico Scientifics, Mumbai.	L1610
3.	Electronic Balance	Shimadzu, Japan.	BL-220H
4.	Friability Apparatus	Veego scientific, Mumbai.	VFT-DV
5.	FTIR Spectrophotometer	Shimadzu, Japan.	S4008
6.	Hardness Tester	Monsanto.	-
7.	Hot Air Oven	Chemi Equipments, Bombay.	P-1401
8.	Humidity Chamber	Labtech, Ambala.	_
9.	Melting Point Apparatus	GUNA Enterprises, Chennai.	_
10.	Sixteen stage tablet Compression Machine	Cadmach, Ahmadabad, India.	JMD-4-8
11.	Standard Sieve (20 and 40#)	Jayant scientific, India.	_
12.	USP Tablet Disintegration Apparatus	Veego scientific, Mumbai.	VTD-DV
13.	USP Tablet Dissolution Apparatus Type II	Veego scientific, Mumbai.	VDA-8DR
14.	UV Spectrophotometer	Shimadzu, Japan.	UV Pharmaspec 1700
15.	Vernier Caliper	Indolab, Mitutoyo.	-

EXPERIMENTAL WORK

7.EXPERIMENTAL WORK

7.1. PRELIMINARY STUDIES:

The preliminary studies include testing of different physical and chemical properties of drug including its purity.

7.1.1. Identification of Drug:

7.1.1.1. Identification by FTIR Spectroscopy: (Skoog D.A. et al., 1996; Robert M. Silverstein and Fransis S. Webster, 2003)

The FTIR Spectrum was generally used as an identification by the chemical structure of a compound.

A small quantity of sample was mixed with sufficient potassium bromide and compressed into a pellet by applying a 10 tons pressure with help of a hand operated press. This pellet was kept in a sample holder and scanned from 4000 to 400 cm^{-1}.

7.1.1.2. Identification by Melting Point: *(IP, 2007)*

It was a simple primary physical test tested to test the purity of the drug. This parameter was analyzed by use of a laboratory melting point apparatus (Guna enterprises, Chennai) with a procedure stated in the Indian Pharmacopoeia, 2007.

7.1.2. Physico-chemical Parameters:

7.1.2.1.OrganolepticProperties: (Lachman.L.et al.,1991)

The Organoleptic properties like physical state, color, odor etc., of the drug were reported with help of the descriptive terminology. The drug is identified by a simple procedure.

7.1.2.2. Solubility Study: *(IP, 2007)*

The solubility of pure drug was determined in various solvents in order to select the solvents for the various analytical progresses and it is also important in the

therapeutic response. The solubility of drug was tested by micropipette method and results were reported by using various descriptive terminology specified in IP, 2007.

7.1.3. Analytical Methods:

7.1.3.1. Determination of λ max (Shankar Avulapati .et al.,2011)

The absorption maximum of the standard solution was scanned between 200-400 nm regions on Shimadzu-1700 UV spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in the position.

7.1.3.2. Preparation of standard graph of Losartan potassium

7.1.3.2.1. Preparation of solutions:

7.1.3.2.2. Preparation of p^H 6.8 phosphate buffer: *(IP, 2007)*

Phosphate buffer p^H 6.8 was prepared according to I.P. 2007. Placed 50ml of 0.2M potassium dihydrogen phosphate in a 200ml volumetric flask and 22.4ml of 0.2M sodium hydroxide was added and volume was made upto required quantity with water.

7.1.3.2.3. Preparation of stock solution of Losartan potassium with p^H 6.8 phosphate buffer:

Accurately weighed 25 mg of Losartan potassium was dissolved in little quantity of p^H 6.8 buffer solution and volume was made upto 25ml,from that solution 10ml was adjusted to 100ml with phosphate buffer to prepare standard solution.

7.1.3.2.4. Procedure:

From the stock solution, aliquots of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4 ml were transferred to 25 ml volumetric flasks and final volume was made to 25 ml with p^H 6.8 phosphate buffer. Absorbance values of these solutions were measured against blank (pH 6.8 buffer) at 206nm using Shimadzu-1700 UV spectrophotometer.

7.2. DETERMINATION OF DRUG AND EXCIPIENTS COMPATIBILITY:

(Robert M. Silverstein and Fransis S., 2003)

It is a primary identification test to know the compatibility of the drug with the excipients used in the formulation. Some substances, like talc flavors etc., used in the formulation does not need to check the compatibility because of their inertness. There are so many methods to report the compatibility out of that FTIR and DSC studies were taken into consideration to check and report the compatibility.

7.2.1. Fourier transforms Infra-Red (FTIR) spectroscopy (*IP, 2007)*

FTIR study was carried out to check compatibility of drug with polymers. Infrared spectrum of Losartan potassium was determined using Spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using Parkin elmer-Pharmaspec-1 FTIR spectrophotometer.

7.2.2. Differential Scanning Calorimetry (DSC):

Differential scanning calorimetry **(**Shimadzu, Japan) was used to examined the thermal behaviour of pure drug and drug additive mixtures. Compatibility studies were carried on samples of 1:1 physical mixtures of the drug(Losartan Potassium) with various excipients viz...crosspovidone, avicel etc. The 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30 ml/min.

7.3. PREPARATION AND EVALUATION OF POWDER BLEND:

(Nagendrakumar D. et al., 2009; Swamy P.V et al., 2009)

7.3.1. Preparation of Powder Blend:

All the ingredients mentioned in Table 7.3 were weighed and sifted through #44 mesh separately (crosspovidone and avicel made anhydrous by heated at a temperature of 60ºC for 30 minutes in hot air oven). The ingredients after sifting through sieve No. 44 were thoroughly blended except magnesium stearate in mortar and pestle for 15 min. Finally magnesium stearate was added as a lubricant and mixed thoroughly, and then each powder blend was stored in polythene bag individually. The batch size for each powder blend was 100 tablets. The prepared powder blends were evaluated for micromeritic properties before tablet compression.

7.3.2. Evaluation of Micromeritic Properties of Powder Blend:

(Lachman L. et al., 1987; Aulton M.E., 2007; Ansel S.C. et al., 2009 , Shankar Avulapati .et al.,2011*)*

7.3.2.1. Angle of Repose:

It was “an indirect method for the determination of flowability of powder/ granules”, because of their relationship with the inter-particulate cohesion.

Table 7.1 Relationship between Angle of Repose and Flowability

S. No.	Angle of Repose(°)	Flowability
1.	< 25	Excellent
2.	25 - 30	Good
3.	30 - 40	Passable
4.	37 - 45	Poor
5.	> 45	Very Poor

Method:

A funnel was fitted to a burette stand at a distance of 8cm to 10cm from the horizontal plane to the brim. The test sample was filled in the funnel and made allowed through the small opening of funnel on a graph sheet. The flow forms a pile/cone on the graph paper. The height and radius of pile were measured by help of a scale. Angle of Repose (θ) was calculated with help of the following formula:

$$\tan(\theta) = \frac{h}{r}$$

Where, 'h' is the height of the pile

'r' is the radius of the pile

7.3.2.2. Bulk Density and Tapped Bulk Density:

Bulk Density was defined as "the ratio of mass of a powder/granules and the bulk volume of powder/granules". It also called as Loose Bulk Density (LBD).

Tapped Bulk Density (TBD) was defined as "the ratio of the mass of a powder/granules and the tapped volume of powder/granules".

These parameters are primarily effect by different parameters like the distribution of same size particles, shape of particles, and adherence of particles with other.

Method:

An accurately weighed quantity of powder from each formulation was passed through the sieve #40 with light shaking (to break any agglomerates formed in mixing).

Then the blend was introduced into a graduated cylinder. After the initial volume was observed, the cylinder was allowed to tap in away as it moves under its own weight onto a hard flat surface from the height of 2.5 cm at two second intervals.

The tapping was continued until no further change in volume was noted as tapped volume.

LBD and TBD were calculated using the following formulas:

$$\text{Loose Bulk Density} = \frac{\text{Total Weight of Powder}}{\text{Total Volume of Powder}}$$

$$\text{Tapped Bulk Density} = \frac{\text{Total Weight of Powder}}{\text{Total Volume of Tapped Powder}}$$

7.3.2.3. Bulkiness:

This parameter was to check uniformity of bulk chemicals. The bulkiness was determined by using following formula,

$$\text{Bulkiness} = \frac{1}{\text{Loose Bulk Density}}$$

7.3.2.4. Hausner's Ratio:

Hausner's Ratio was defined as "ratio of tapped bulk density and loose bulk density". It was determined by following equation,

$$\text{Hausner's Ratio} = \frac{\text{TBD}}{\text{LBD}}$$

Where, TBD is Tapped Bulk Density

LBD is Loose Bulk Density

A Hausner's Ratio less than 1.2 indicates good flow while greater than 1.6 indicates poor flow of powders.

7.3.2.5. Carr's Compressibility Index:

Compressibility was an important measure that can be obtained from the LBD and TBD. The compressibility index of the granules was determined by Carr's Compressibility Index. It can be determined by following formula,

$$\text{Carr's Compressibility Index}\,(\%) = \frac{(\text{TBD} - \text{LBD})}{\text{TBD}} \times 100$$

Where, TBD is Tapped Bulk Density

LBD is Loose Bulk Density

The relationship of flow with the Carr's Compressibility Index was depicted in Table 7.2.

Table 7.2 Relationship between Carr's Compressibility Index and Flowability

S. No.	Carr's Compressibility Index (%)	Type of Flow
1.	5 - 15	Excellent
2.	12 - 16	Good
3.	18 - 21	Fair to Passable
4.	23 - 35	Poor
5.	33 - 38	Very Poor
6.	> 40	Extremely Poor

7.4. FORMULATION:

7.4.1. Preparation of Porous Tablets: *(Swamy P.V. et al., 2009; Ravi kumar et al., 2008; Kaushik D. et al., 2004)*

The Porous Tablets of (25mg Losartan potassium) were prepared by direct compression.

Formula for different formulations of Losartan potassium Porous Tablets was listed in Table 7.3.

The powder blend was directly compressed into tablets having average weight of 200mg using a sixteen station tablet punching machine (Cadmach, Ahmedabad, India.) fitted with 9 mm round, one side break line flat punches.

Due to presence of the hygroscopic materials (Sublimation agents) the de-humidifier was used throughout the compression time to maintain the desired humidity conditions in the compression room.

The die capacity was adjusted in order to get a 200 mg Porous Tablet and the compression force was kept as constant to produce hardness of the tablets at 2.5 kg/cm^2.

Table 7.3 Formulation Table of Porous Tablets of Losartan potassium

S. No.	Ingredients (mg)	Formulation Code with Quantities in mg								
		FT1	**FT2**	**FT3**	**FT4**	**FT5**	**FT6**	**FT7**	**FT8**	**FT9**
1.	Losartan potassium	25	25	25	25	25	25	25	25	25
2.	Camphor	25	50	-	-	-	-	-	-	-
3.	Ammonium bicarbonate	-	-	25	50	-	-	-	-	-
4.	Menthol	-	-	-	-	25	50	-	-	-
5.	Thymol	-	-	-	-	-	-	25	50	-
6.	Avicel	5	5	5	5	5	5	5	5	5
7.	Mannitol	126	101	126	101	126	101	126	101	151
8.	Crosspovidone	5	5	5	5	5	5	5	5	5
9.	Talc	2	2	2	2	2	2	2	2	2
10.	Aspartame	5	5	5	5	5	5	5	5	5
11.	Magnesium Stearate	4	4	4	4	4	4	4	4	4
12.	Pineapple flavor	3	3	3	3	3	3	3	3	3
Total Weight		200	200	200	200	200	200	200	200	200

7.5. EVALUATION:

7.5.1. Evaluation of porous tablets:

7.5.1.1. Appearance *(Lachman L.,et al.,1991; Bankar G.S. and Rhodes C.T.,1996)*

The tablets were visually observed for capping, chipping, lamination and colour.

7.5.1.2. Thickness and Diameter Test: *(IP, 2007)*

Thickness and Diameter test permits accurate measurement and provides information on the variation between tablets. Ten tablets were taken and the thickness and diameter was measured using a vernier caliper. The tablet thickness and diameter should be controlled within a 5% variation of a standard value.

7.5.1.3. Weight Variation Test: *(IP, 2007)*

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. The specifications were given in Table 7.4.

Table 7.4 Specifications of %Weight Variation Allowed in Tablets as per Indian Pharmacopoeia

S. No.	Average Weight of Tablets (mg)	Maximum Percent Deviation Allowed (%)
1.	80 or less	10
2.	More than 80 but less than 250	7.5
3.	More than 250	5

7.5.1.4. Hardness Test: *(IP, 2007)*

Hardness indicates “the ability of a tablet to withstand mechanical shocks while handling”. The hardness of the tablets was determined using Monsanto

Hardness Tester. The force needed to disrupt them by crushing in kg/cm^2 expresses it. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

7.5.1.5. Friability Test: *(IP, 2007)*

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using Roche Friabilator.

Tablets about 20nos were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The % friability was then calculated by,

$$\%F = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Percent friability of tablets less than 1% are considered as acceptance.

7.5.1.6. Assay: (IP, 2007)

Content uniformity was determined by accurately weighing 20 tablets and crushing them in mortar. Then an accurately weighed quantity of powder equivalent to 20 mg of drug was transferred to a 100 ml volumetric flask. Few ml of water was added and shaken for 15 min. Volume was made up to 100 ml with distilled water. The solution was filtered through Whatmann filter paper. 5 ml of the filtrate was diluted to 100 ml with p^H 6.8 phosphate buffer. Then absorbance of the resulting 10 µg/ml solution was recorded at 206nm from which conent of drug was calculated.

7.5.1.7. Content Uniformity: *(USP, 2009)*

This test is applicable to tablets that contain equivalent or less than 10 mg or less than 10% w/w of active ingredient. The test content uniformity carried out by taking the 5 individual tablets from each formulation batch and in that selected tablets the drug content was calculated by the procedure given in the assay of Porous Tablets individually.

7.5.1.8. In-Vitro Disintegration Time: *(Na Zhao et al., 2005;* Shankar Avulapati .et al.,2011, *USP, 2009)*

This test was performed to ensure disintegration of tablets in saliva. For the determination of In-Vitro disintegration time six tablets were randomly selected from each formulation and one tablet is introduced in to one tube of USP disintegration test apparatus and a disc was added into the each tube. The assembly was then suspended in the beaker containing pH 6.8 phosphate buffer solution. The tubes were then raised and lowered through a distance of 5.3 to 5.7 cm in buffer solution maintained at 37° ± 2°C. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds. The average time of six tablets to complete disintegration was reported as in-vitro disintegration time. The test was carried out by using United States Pharmacopoeia (USP) Disintegration Test Apparatus model Veego VTD-DV.

7.5.1.9. Simulated Wetting Time (SWT): *(Jae Han Park et al., 2008)*

The wetting time of the ODTs was evaluated using the method described below. The method is called the "Simulated Wetting Test". One Whattman filter paper disc (21 mm in diameter) was placed in each well of a cup (22 mm in diameter). A volume 1.25 ml of 0.1% (w/w) Sensient Blue Dye solution was then added into cup.A rapimelt Tablet was carefully placed on the surface of the wet paper disk in cup using

a pair of forceps. The flat tablet face was in contact with the filter paper, and the level of the dye solution did not cover the tablet. The total wetting time was measured, defined as the time required for the blue dye solution to diffuse through the tablet and completely cover the surface. The wetting time was recorded as the simulated disintegration time.

7.5.1.10. In-Vitro Dissolution Study: (*IP, 2007;USP 2007; Lachman L.,et* al.,1991; Shankar Avulapati .et al , Yeole P.G., et al., 2006)

The in vitro dissolution was carried out using USP type II dissolution apparatus was determined using USP Dissolution testing apparatus type-II (Paddle method; Veego Scientific VDA-8DR, Mumbai, India).

Dissolution medium: pH 6.8 phosphate buffer for 30 minutes.

Dose size: 25mg.

Average weight of tablet: 200mg.

Volume of medium: 900ml.

Speed of paddle: 50 rpm.

Temperature of dissolution medium: 37± 1^0 C.

The tablets were placed in the dissolution medium and the apparatus was operated. At predetermined time intervals of 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10 hours 5 ml aliquots were withdrawn and replacement was done each time with equal amounts of fresh dissolution medium maintained at same temperature. Each 5 ml aliquot was filtered through Whatman filter paper (No.41). 5 ml of sample was diluted to 10 ml pH 6.8 phosphate buffer for 30 minutes and absorbance of these solutions was measured at 206 nm using a Shimadzu-1700 UV spectrophotometer. Drug concentrations in the

sample were determined from standard calibration curve. The release data were calculated by using PCP disso V3 software.

7.6. KINETICS OF *IN-VITRO* DRUG RELEASE OF POROUS TABLETS

(Brahmankar D.M. et al., 2009; Suvakanta Dash et al., 2010)

To study the release kinetics of *in-vitro* drug release, data was applied to kinetic models such as Zero Order, First Order, Higuchi, Korsmeyer Peppas.

Zero Order

$$C = K_0 t$$

Where, 'K_0' - zero-order rate constant expressed in units of concentration/time

't' - time in hours

First Order

$$\text{Log } C = \text{Log} C_0 - Kt / 2.303$$

Where, 'C_0' - initial concentration of drug

'K' - first order constant

't' - time in hours

Higuchi

$$Q_t = Kt^{1/2}$$

Where, 'Q_t' - amount of the release drug in time t

'K' - kinetic constant

Korsmeyer Peppas

$$M_t / M_\infty = Kt\ n$$

Where, 'M_t' - represents amount of the released drug at time t

'M_∞'- overall amount of the drug (whole dose) released

'K' - diffusional characteristic of drug/ polymer system constant

'N' - diffusional exponent that characterizes the mechanism of drug release

7.7. STABILITY STUDY: *(Janes T. Garnsten and Rhodes C.T., 2000; Manavalan R. and Ramasamy S., 2004)*

The test was performed according to the International Conference on Harmonization Guidelines titled "Stability Testing of New Drug Substances". The Porous Tablets formulation were well packed in aluminium foils and stored at 40°C ± 2°C at 75% RH ± 5% RH for accelerated temperature conditions for 3 months. The samples were withdrawn after periods of 1st month, 2nd month and 3rd month. The samples were analyzed for different characteristics to evaluate the changes occurred in the stability period.

RESULTS AND DISCUSSION

8.RESULTS AND DISCUSSION

8.1. PREFORMULATION PARAMETERS

8.1.1. physicochemical parameters of drug

8.1.1.1. Organoleptic properties

Odourless, white or almost white crystalline powder.

8.1.1.2. Melting point

Melting point values of Losartan potassium sample was found to be in range of 185^0C to 189^0C. The reported melting point range for Losartan potassium was 185.5^0C to 186^0C. Hence, experimental values were in good agreement with official values.

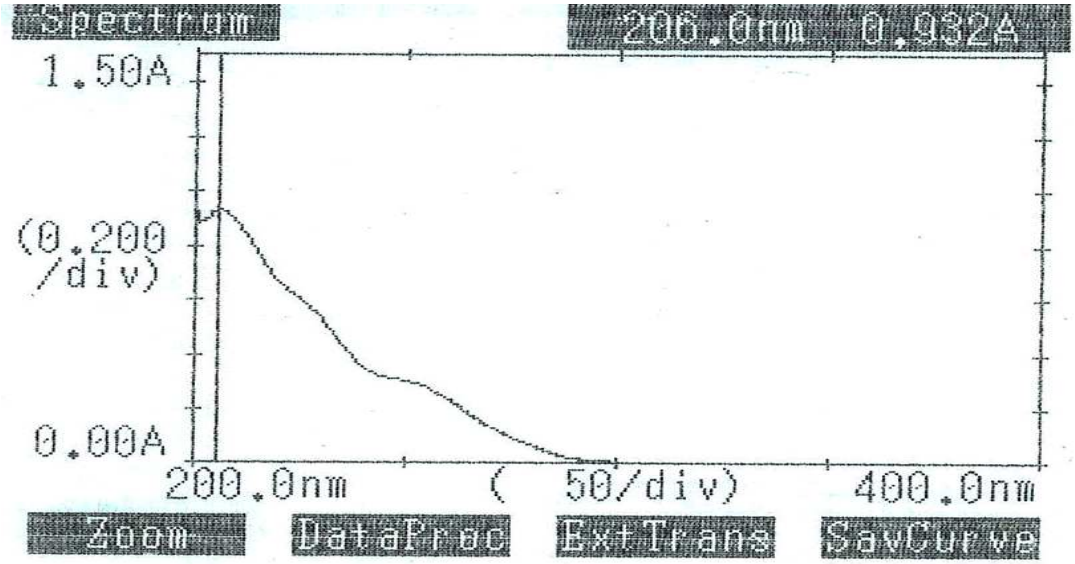
8.1.1.3. Solubility study

Table 8.1: The solubility of Losartan potassium in various solvents

Name of solvent	Inference
Distilled water	Freely soluble
Methanol	Very soluble
Iso propyl alcohol	Soluble
Acetonitrile	Sparingly soluble
Acetone	Slightly soluble
Chloroform	Slightly soluble
0.1N HCl	Slightly soluble
Phosphate buffer(pH6.8)	Soluble

8.1.2. Analytical methods

8.1.2.1.λmaxDetermination



The absorption maximum for Losartan potassium was found to be 206 nm.

Figure 8.1: λ max observed for Losartan potassium in p^H 6.8 Phosphate buffer.

8.1.2.2. Preparation of standard graph of Losartan potassium

8.1.2.3. Preparation of standard graph of Losartan potassium in p^H 6.8 Phosphate buffer.

UV absorption spectrum of Losartan potassium in p^H 6.8 Phosphate buffer shows λ max at 206nm. Absorbances obtained for various concentrations of Losartanpotassium in p^H 6.8 phosphate buffer are given in table no.8.2 and graph was graphically represented in figure 8.2. The graph of absorbance vs concentration for Losartan potassium was found to be linear in the concentration range of 2-16 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-16 µg /ml.

Table 8.2: Data of concentration and absorbance for Losartan potassium in p^H 6.8 phosphate buffer.

S.No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	2	0.219
3	4	0.435
4	6	0.605
5	8	0.812
6	10	0.991
7	12	1.183
8	14	1.381
9	16	1.574

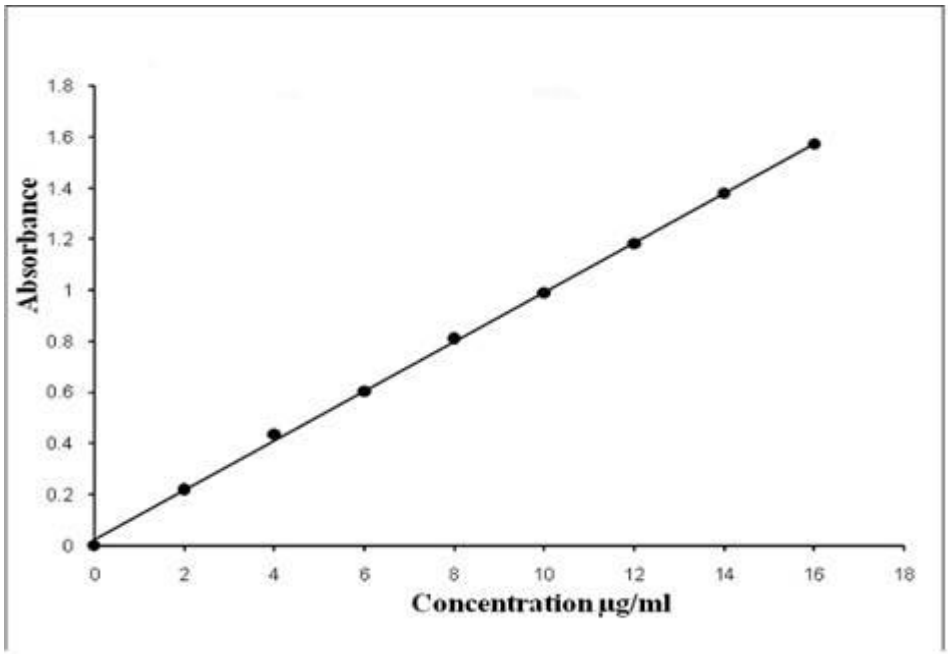


Figure 8.2: Standard graph of Losartan potassium in p^H 6.8 Phosphate buffer**.**

Table 8.3: Data for calibration curve parameters

S. No.	Parameters	Values
1	Slope (m)	0.0972
2	Intercept(c)	0.0224
3	Correlation coefficient (R)	0.9997

8.1.2.3. Percentage purity of pure Drug

The percentage purity of drug was calculated by using calibration graph method (least square method) was shown in table 8.4.

Table 8.4: Percentage purity of pure drug

S. No.	Percentage purity (%)	Avg. percentage purity (%)
1	100.02	99.35
2	99.30	
3	99.40	

The reported percentage purity for Losartan potassium is 98 to 102% (I.P. 1996).

8.1.3. Compatibility testing of drug with polymer

8.1.3.1. Fourier transforms Infra-Red (FTIR) spectroscopy

FTIR study was carried out to check compatibility of drug with polymers. Infrared spectrum of Losartan potassium was determined on fourier transform infrared spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using Parkin elmer-Pharmaspec-1 FTIR spectrophotometer.All the FTIR spectrum were shown in figure 8.3-8.6.

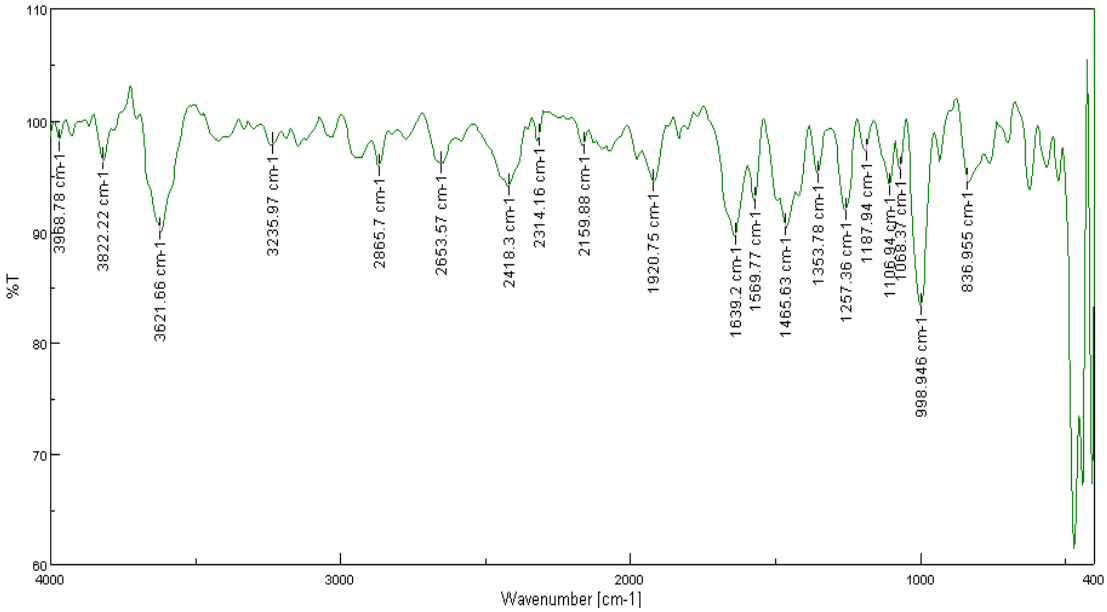


Figure 8.3: FTIR spectra of Losartan potassium

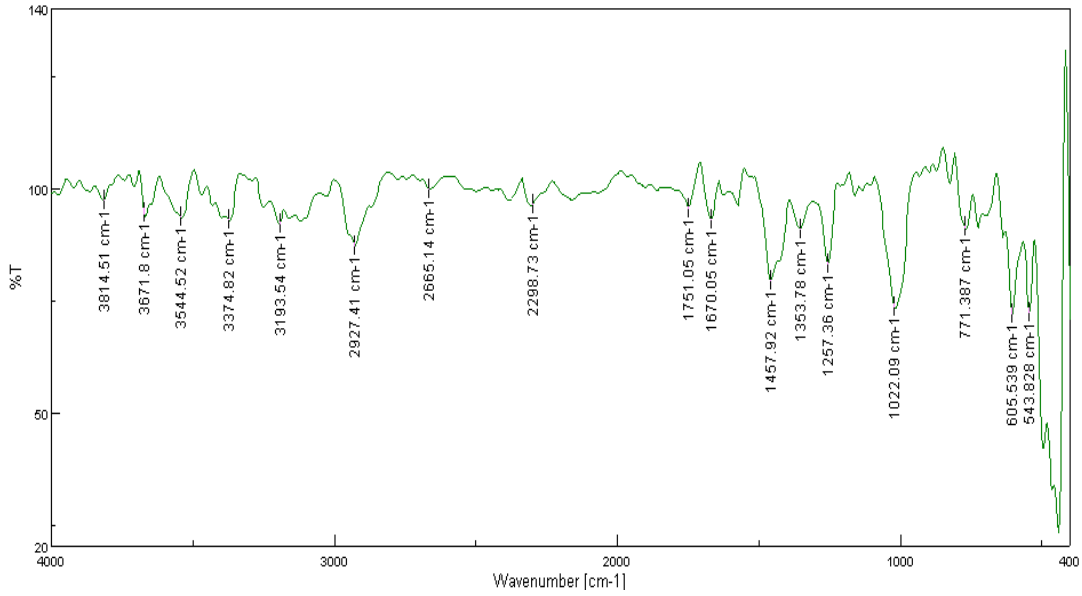


Figure 8.4: FTIR spectra of Losartan potassium and Avicel

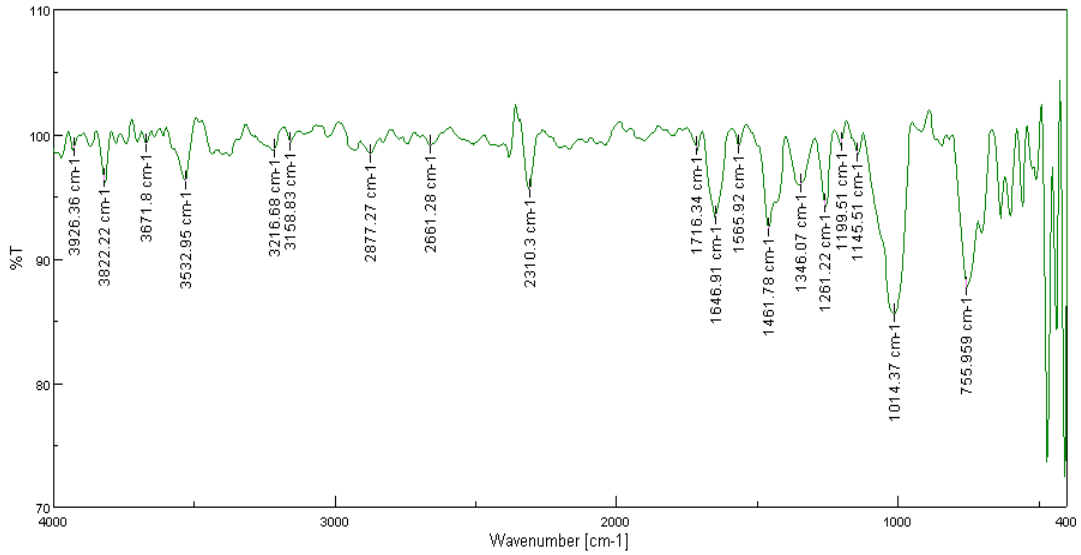


Figure 8.5: FTIR spectra of Losartan potassium and crosspovidone

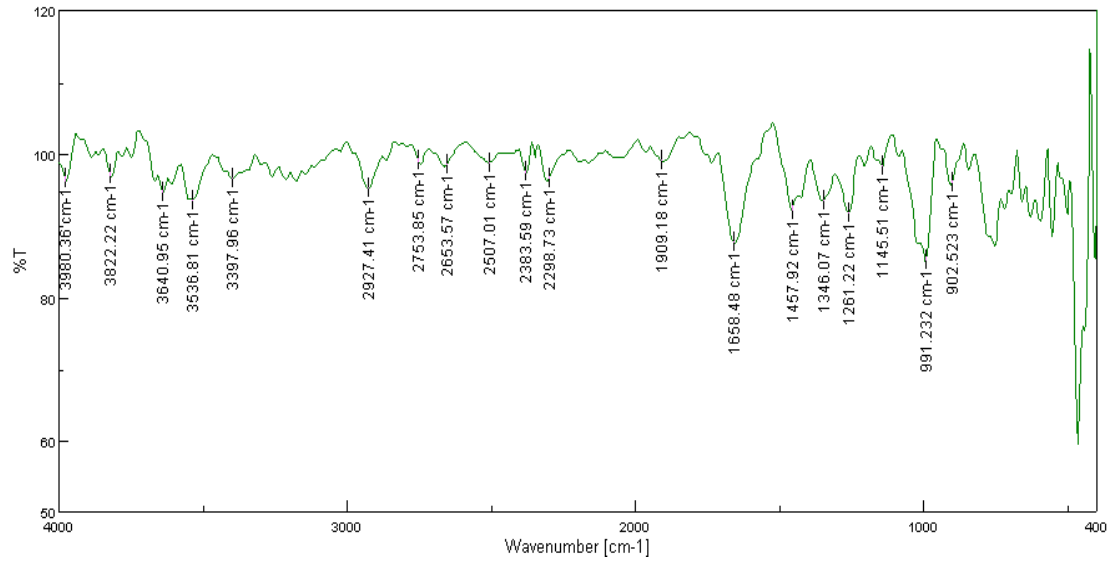


Figure 8.6: FTIR spectra of Losartan potassium and mannitol

Interpretation of FTIR Spectrum

Table 8.5: Data for characteristic frequencies in FTIR spectrum of Losartan potassium

Wave no.(cm^{-1})	Inference
2865.7	C-H stretching
1465.63	C-H bending
3621.66	O-H stretching
1187.94	C-O stretching
1353.78	O-H bending
1257.36	C-H Methylene bending
1068.37	Cl-Group
1485.63	C-C m ring stretching

Major functional groups present in Losartan potassium showed characteristic peaks in IR spectrum. Table 8.5 shows peaks observed at different wave numbers and their functional group associated with these peaks. The major peaks were identical to functional group of Losartan potassium. Hence, the sample was confirmed as Losartan potassium.

8.1.3.2) Differential Scanning Calorimetry (DSC)

The compatibility and interactions between drugs and polymer were checked using differential scanning calorimetry (DSC) results obtained were shown in Figure 8.7- 8.10 and Table 8.6

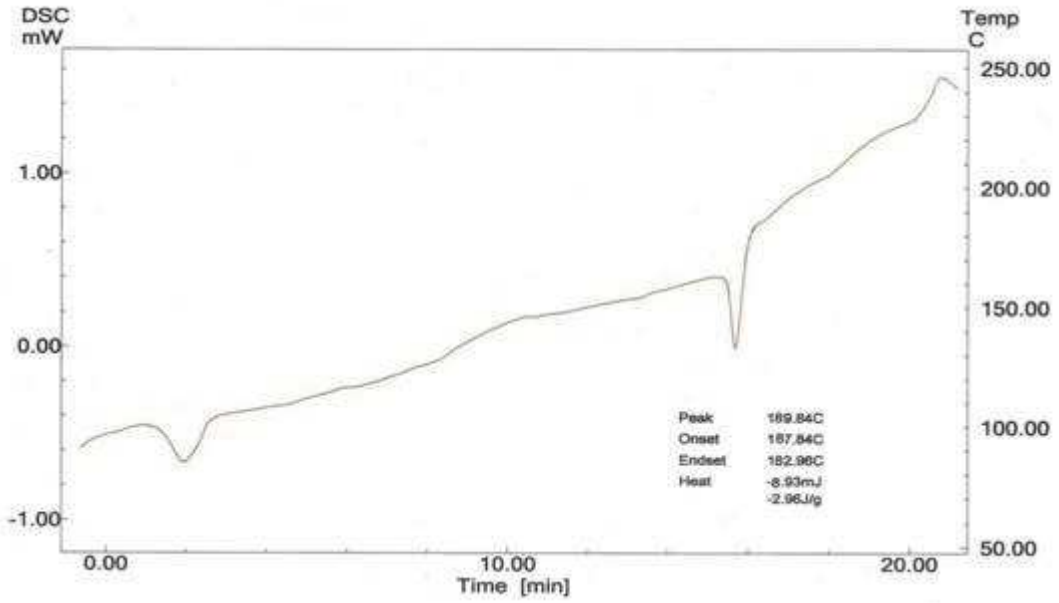


Figure 8.7: DSC thermal analysis of pure Losartan potassium

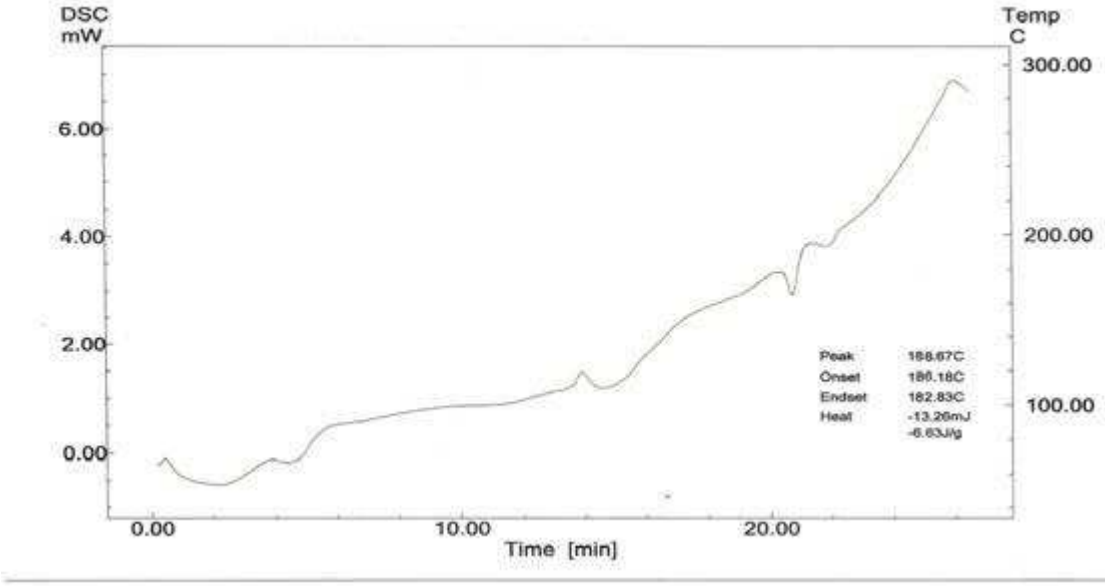


Figure 8.8: DSC thermal analysis of Losartan potassium+ avicel

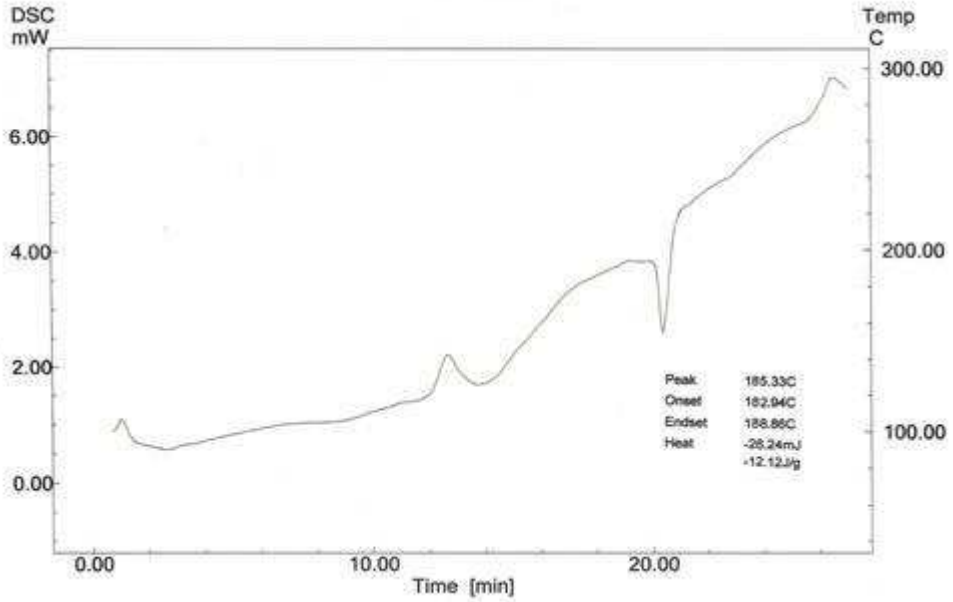


Figure 8.9: DSC thermal analysis of Losartan potassium + cross povidone

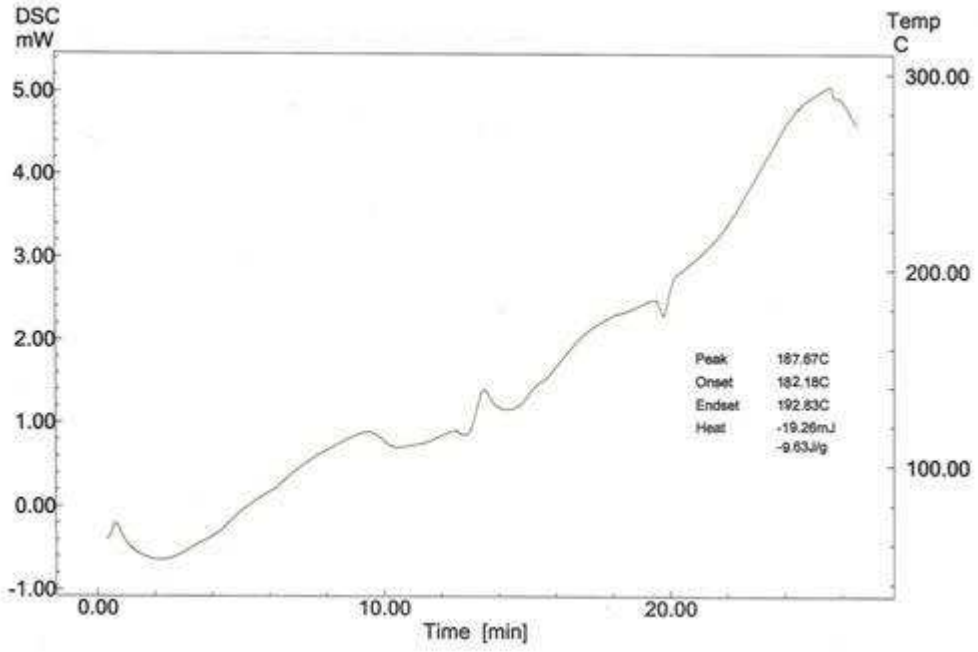


Figure 8.10: DSC thermal analysis of Losartan potassium + mannitol

Table 8.6: Data for DSC thermogram parameters

Sr. No.	DSC thermogram sample	Onset temperature(°C)	Peak temperature(°C)
1	Pure Losartan potassium	187.84	189.84
2	Losartan potassium + avicel	186.18	188.67
3	Losartan potassium + crosspovidone	185.33	182.94
4	Losartan potassium+ mannitol	182.18	187.67

DSC thermogram showed that there was no interaction found between drug and polymers.

8.1.4. Characterization of powder blend

The powder blends were prepared by mixing of various ingredients mentioned in table 8.7 and used for characterization of various flow properties of powder.

Table 8.7: Flow properties of powder

F Code	Bulk density (g/cm^3)*	Tapped bulk density (g/cm^3)*	Hausner ratio (HR)*	Carr's index (IC)*	Angle of repose (θ)*
F1	0.555±0.000	0.666±0.000	1.200±0.00	16.66±0.00	30.212±0.58
F2	0.566±0.015	0.700±0.048	1.235±0.05	18.95±0.23	28.697±0.01
F3	0.588±0.000	0.734±0.048	1.248±0.08	19.59±0.51	28.522±0.00
F4	0.546±0.029	0.652±0.019	1.195±0.05	16.20±0.78	29.557±0.61
F5	0.545±0.013	0.638±0.019	1.171±0.03	12.88±0.06	29.561±0.45
F6	0.476±0.000	0.600±0.017	1.219±0.02	20.64±0.25	30.988±0.42
F7	0.546±0.029	0.652±0.019	1.195±0.05	16.20±0.82	28.682±0.64
F8	0.545±0.013	0.625±0.000	1.146±0.02	12.72±0.16	25.412±0.59
F9	0.526±0.000	0.600±0.017	1.140±0.03	12.30±0.49	30.730±0.21

*All the values are expressed as mean± SD, n=3.

8.1.4.1. Bulk Density (BD)

The powder blends bulk density ranged between 0.476±0.000 to 0.588±0.000 gm/ml.

8.1.4.2. Tapped bulk density (TBD)

The powder blends tapped bulk density range between 0.600±0.017 to 0.734±0.048 g/ml. These values indicate good packing characteristics and the powder was not bulky.

8.1.4.3. Carr's Compressibility Index

The carr's index for all the formulations was found to be below 12% indicating that the powders have a excellent compressibility.

8.1.4.4. Hausner's Ratio

The hausner ratio for all the formulations was found to be <1.25, indicating good flow properties.

8.1.4.5. Angle of repose

The flow properties of granules were analyzed by determining angle of repose which was found to be between 25.412±0.59 to, indicating 30.730±0.21 excellent flow property.

8.2. EVALUATION OF POROUS TABLET

8.2.1. Appearance

The tablets were observed visually and did not show any defect such as capping, chipping and lamination.

8.2.2. Physical characteristic

The physical characteristic of Losartan potassium porous tablets formulations (F1 to F9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations (F1 to F9) found to be within the limits specified in official books as per I.P.

8.2.2.1. Dimension (Thickness and Diameter)

Table 8.8: Physico-chemical characterization of Losartan potassium porous tablets:

F Code	Dimension		Hardness (kg/cm^2)*	Friability (%)*	Weight variation (%)	Drug content (%w/w)*
	Diameter (mm)*	Thickness (mm)*				
F1	8.0±0.0	3.00±0.00	2.10±0.000	0.590±0.02	1.448	100.80±0.2
F2	8.0±0.0	3.00±0.00	2.10±0.020	0.632±0.25	1.139	99.47±0.4
F3	8.0±0.0	3.00±0.00	2.16±0.012	0.697±0.12	1.799	100.72±0.1
F4	8.0±0.0	3.00±0.00	2.09±0.008	0.805±0.18	1.162	100.03±0.8
F5	8.0±0.0	3.00±0.00	2.13±0.026	0.668±0.13	1.123	99.55±0.95
F6	8.0±0.0	3.00±0.00	2.12±0.008	0.688±0.23	1.755	100.14±0.9
F7	8.0±0.0	3.00±0.00	2.10±0.004	0.486±0.12	1.440	100.5±0.68
F8	8.0±0.0	3.00±0.00	2.08±0.004	0.667±0.07	1.406	99.37±0.5
F9	8.0±0.0	3.00±0.00	2.10±0.000	0.454±0.07	0.655	98.59±0.7

*All the values are expressed as mean± SD, n=3.

Thickness and diameter specifications may be set on an individual product basis. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. The size (diameter) of the tablets of all formulations were found to be 8.0±0.0 mm and thickness of all formulation was found to be 3.00.

8.2.2.2. Tablet Hardness

A difference in tablet hardness reflects difference in tablet density and porosity. The hardness of tablets was found to be in the range of 2.08±0.004 kg/cm^2 to 2.21±0.020 kg/cm^2. This indicates good tablet strength.

8.2.2.3. Percent Friability

Percentage friability of all the formulations was found between 0.454±0.07to 0.697±0.12%. This indicated good handling property of the prepared porous tablets.

8.2.2.4. Weight Variation

A tablet was designed to contain a specific amount of drug. When the average mass of the tablet is 200 mg the Pharmacopoeial limit for percentage deviation is ± 7.5 %. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the Pharmacopoeial specifications.

8.2.2.5. Drug content of Losartan potassium

The content of active ingredients in the formulation was found to be between 97.54±1.7 to 100.80±1.2 % w/w, which is within the specified limit as per IP 2007(i.e. 90-110% w/w).

8.2.5. In-vitro Disintegration time

Table 8.9 *In-Vitro* Disintegration Time of All porous Formulations

Formulations Code	*In-Vitro* Disintegration Time* (Seconds)
FT1	10.31 ± 0.121
FT2	7.83 ± 0.528
FT3	11.16 ± 0.115
FT4	10.55 ± 0.128
FT5	16.00 ± 0.000
FT6	12.16 ± 0.708
FT7	9.83 ± 0.994
FT8	12.50 ± 0.135
FT9	29.00 ± 0.464

*All the values were expressed as a mean ± SD., n = 3

The disintegration time of all the formulations were found to be within 30seconds, hence the porous tablets disintegration time has been greatly reduced due

to the pores formed by sublimation. The disintegration time of porous tablets of formulation FT1-FT8 has reduced disintegration time compared to FT9.

8.2.6. Simulated Wetting Time:

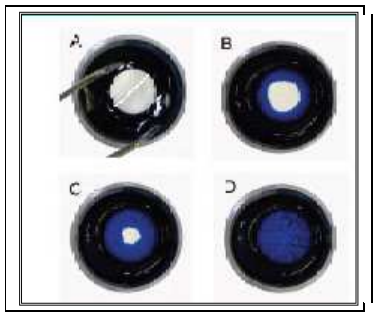


Figure: 8.11 Simulated Wetting Time of Porous tablet at different time intervals A. 0 second, B. 5 seconds, C. 7 seconds D. 9 seconds

Table 8.10 Simulated Wetting Time of All porous Formulations

Formulations Code	Simulated Wetting Time* (s)
FT1	12.00 ± 0.000
FT2	9.00 ± 0.000
FT3	13.33 ± 0.527
FT4	12.00 ± 0.000
FT5	16.00 ± 0.000
FT6	13.00 ± 0.000
FT7	10.33 ± 0.577
FT8	13.66 ± 0.577
FT9	31.33 ± 0.154

***All the values were expressed as a mean ± SD, n = 3.

This test was indirect measurement to identify the disintegration time of the tablet in mouth. The simulated wetting time of porous tablets were reduced compared to nonporous tablets prepared by FT9.This indicates indirectly faster onset action of action of porous tablets. The variations in the disintegration time and stimulated wetting time were due to change in concentrations of excipients added in the tablets.

8.2.7. *In-Vitro* Dissolution profile of porous tablets of Losartan potassium for formulation FT1-FT9

Table 8.11 In-vitro release profile of formulation FT1

S. No.	Time (minutes)	Percentage Drug Released (%)*	Amount of Drug Released (mg)	Dissolution Efficiency (%)	Mean Dissolution Time (minutes)
1.	1	48.32 ± 0.77	7.02	24.16	0.50
2.	3	69.72 ± 0.85	10.13	47.40	0.96
3.	5	83.47 ± 1.09	12.13	59.08	1.46
4.	10	95.53 ± 1.04	13.88	74.29	2.22
5.	20	99.58 ± 0.09	14.47	85.93	2.74
6.	30	-	-	-	-

*All the values were expressed as a mean ± SD, n = 3

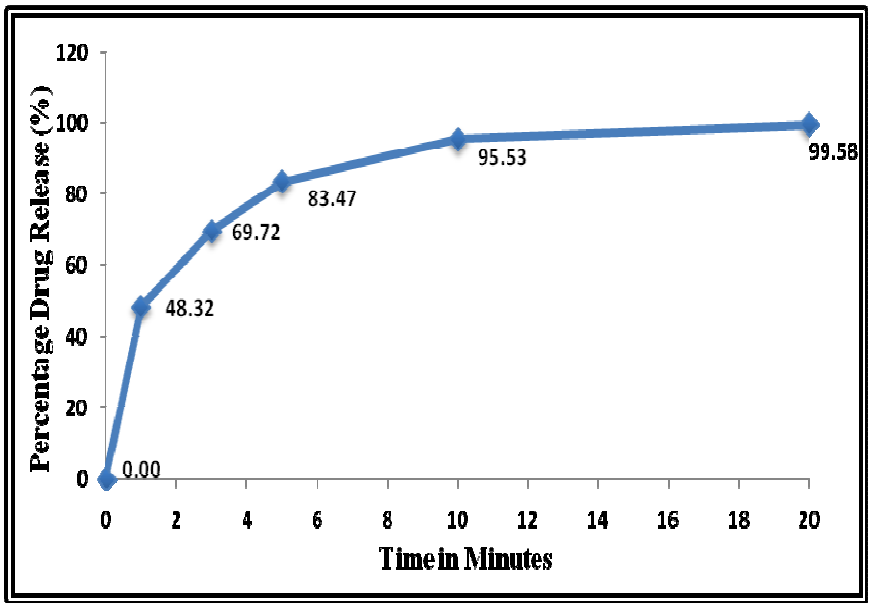


Figure 8.12 In-vitro percentage release of formulation FT1

Table 8.12 In-vitro release profile of formulation FT2

S. No.	Time (minutes)	Percentage Drug Released (%)*	Amount of Drug Released (mg)	Dissolution Efficiency (%)	Mean Dissolution Time (minutes)
1.	1	66.94 ± 1.29	9.73	33.47	0.50
2.	3	91.50 ± 1.34	13.30	63.97	0.90
3.	5	99.09 ± 0.63	14.40	76.50	1.14
4.	10	-	-	-	-
5.	20	-	-	-	-
6.	30	-	-	-	-

*All the values were expressed as a mean ± SD, n = 3

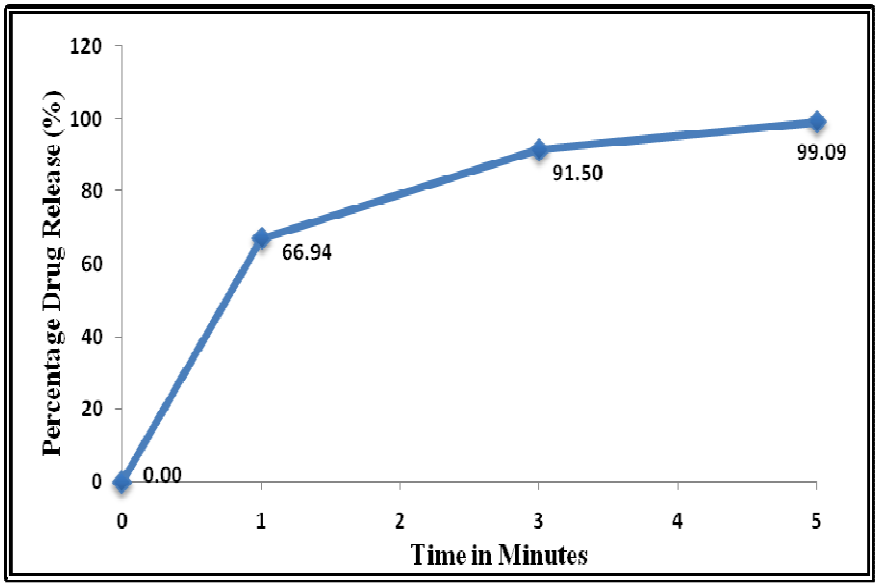


Figure 8.13 In-vitro percentage release of formulation FT2

Table 8.13 In-vitro release profile of formulation FT3

S. No.	Time (minutes)	Percentage Drug Released (%)*	Amount of Drug Released (mg)	Dissolution Efficiency (%)	Mean Dissolution Time (minutes)
1.	1	49.99 ± 0.41	7.26	25.00	0.50
2.	3	71.01 ± 0.34	10.32	48.67	0.94
3.	5	83.18 ± 0.47	12.09	60.04	1.39
4.	10	96.63 ± 0.68	14.04	74.98	2.24
5.	20	99.56 ± 0.11	14.47	86.54	2.62
6.	30	-	-	-	-

*All the values were expressed as a mean ± SD, n = 3

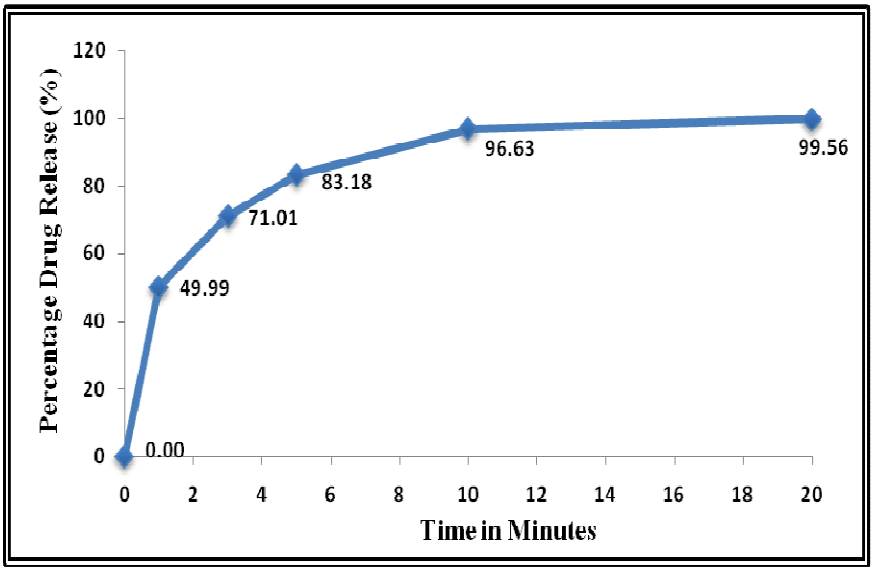


Figure 8.14 In-vitro percentage release of formulation FT3

Table 8.14 In-vitro release profile of formulation FT4

S. No.	Time (minutes)	Percentage Drug Released (%)*	Amount of Drug Released (mg)	Dissolution Efficiency (%)	Mean Dissolution Time (minutes)
1.	1	52.48 ± 0.47	7.63	26.24	0.50
2.	3	71.65 ± 0.35	10.41	50.13	0.90
3.	5	85.54 ± 029	12.43	61.52	1.40
4.	10	99.03 ± 0.36	14.39	76.90	2.23
5.	20	99.65 ± 0.05	14.48	88.13	2.31
6.	30	-	-	-	-

*All the values were expressed as a mean ± SD, n = 3

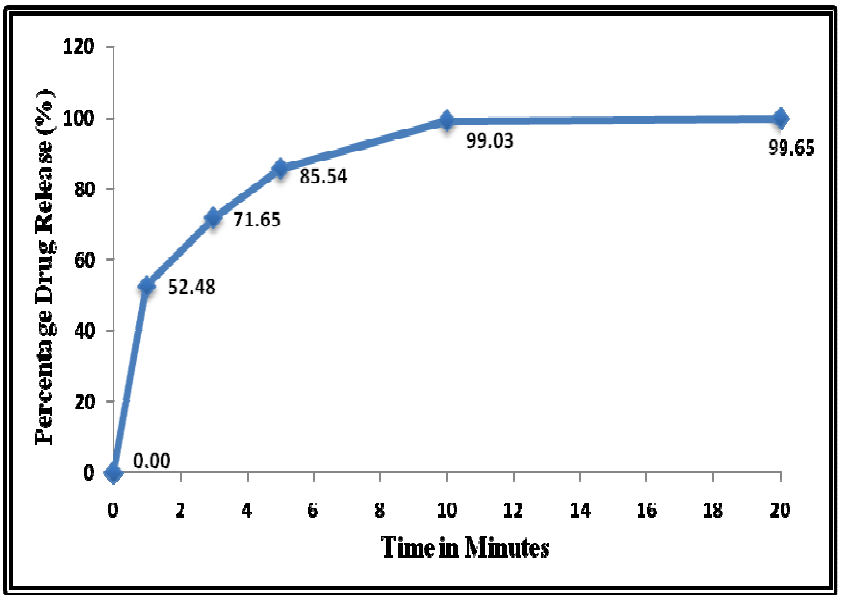


Figure 8.15 In-vitro percentage release of formulation FT4

Table 8.15 In-vitro release profile of formulation FT5

S. No.	Time (minutes)	Percentage Drug Released (%)*	Amount of Drug Released (mg)	Dissolution Efficiency (%)	Mean Dissolution Time (minutes)
1.	1	63.89 ± 1.43	9.28	31.95	0.50
2.	3	88.88 ± 0.79	12.92	61.58	0.92
3.	5	95.30 ± 0.77	13.85	73.79	1.13
4.	10	99.44 ± 0.15	14.45	85.58	1.39
5.	20	-	-	-	-
6.	30	-	-	-	-

*All the values were expressed as a mean ± SD, n = 3

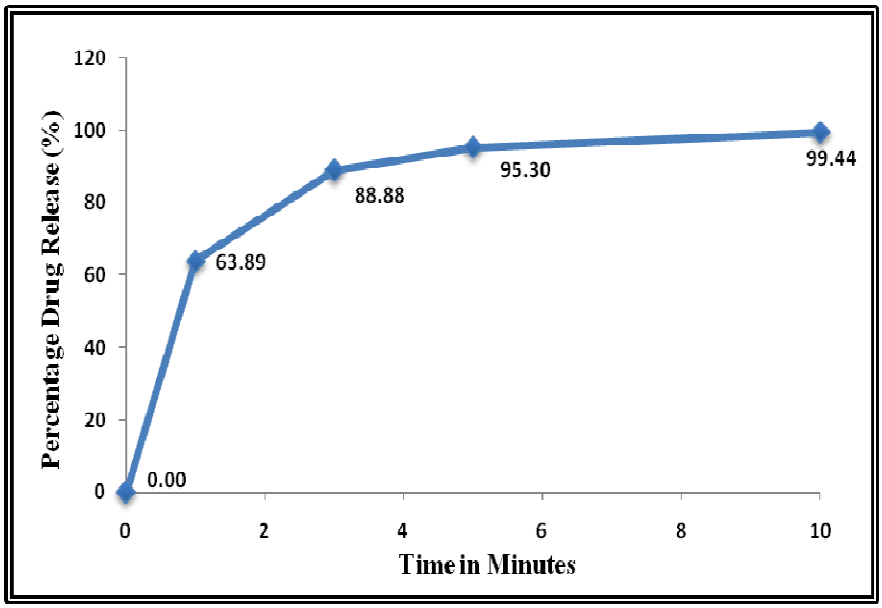


Figure 8.16 In-vitro percentage release of formulation FT5

Table 8.16 In-vitro release profile of formulation FT6

S. No.	Time (minutes)	Percentage Drug Released (%)*	Amount of Drug Released (mg)	Dissolution Efficiency (%)	Mean Dissolution Time (minutes)
1.	1	61.59 ± 0.52	8.95	30.80	0.50
2.	3	87.25 ± 0.91	12.68	59.88	0.94
3.	5	94.81 ± 0.17	13.78	72.34	1.19
4.	10	99.46 ± 0.24	14.45	84.74	1.48
5.	20	-	-	-	-
6.	30	-	-	-	-

*All the values were expressed as a mean ± SD, n = 3

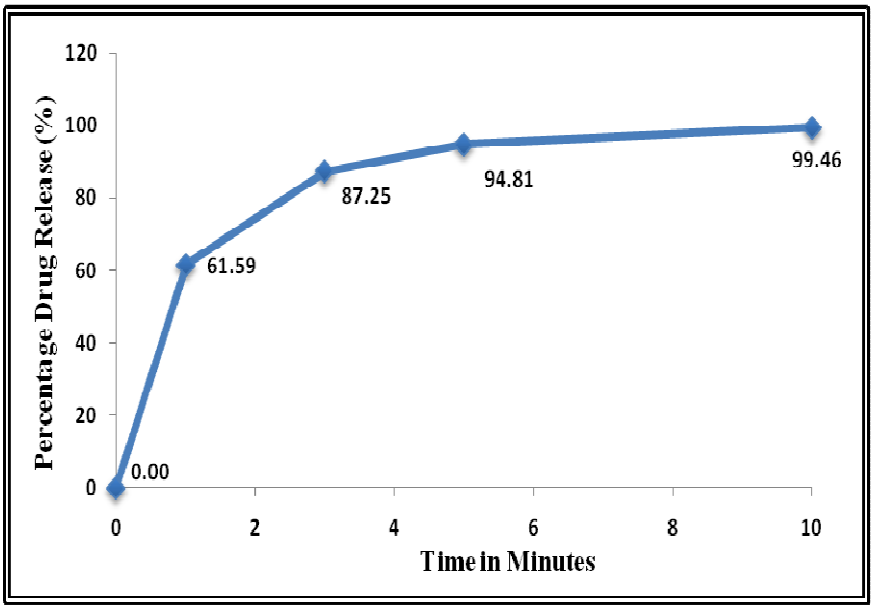


Figure 8.17 In-vitro percentage release of formulation FT6

Table 8.17 In-vitro release profile of formulation FT7

S. No.	Time (minutes)	Percentage Drug Released (%)*	Amount of Drug Released (mg)	Dissolution Efficiency (%)	Mean Dissolution Time (minutes)
1.	1	51.59 ± 0.49	7.50	25.80	0.50
2.	3	80.15 ± 0.16	11.65	52.51	1.03
3.	5	83.85 ± 0.86	12.18	64.31	1.17
4.	10	99.13 ± 0.17	14.40	77.90	2.14
5.	20	99.53 ± 0.08	14.46	88.62	2.19
6.	30	-	-	-	-

*All the values were expressed as a mean ± SD, n = 3

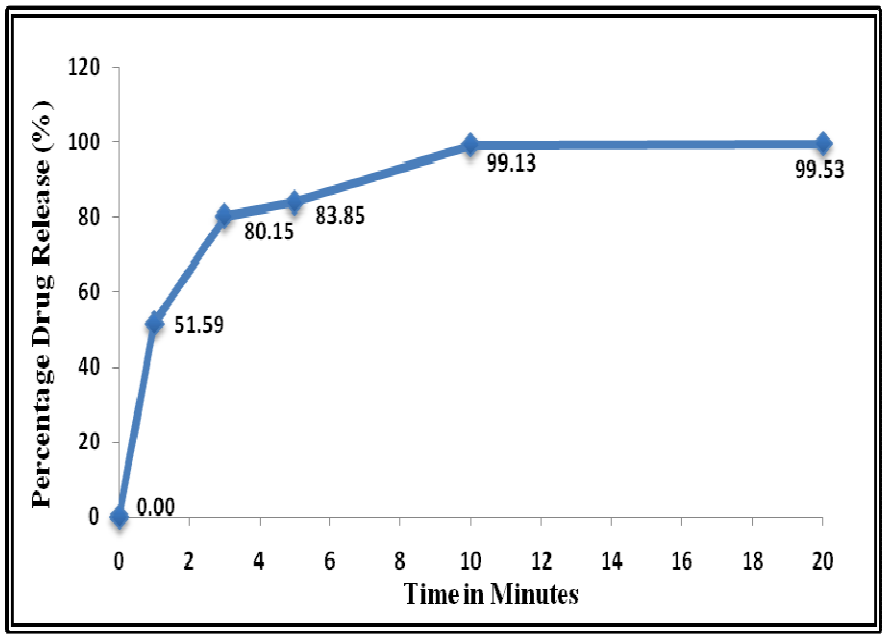


Figure 8.18 In-vitro percentage release of formulation FT7

Table 8.18 In-vitro release profile of formulation FT8

S. No.	Time (minutes)	Percentage Drug Released (%)*	Amount of Drug Released (mg)	Dissolution Efficiency (%)	Mean Dissolution Time (minutes)
1.	1	51.31 ± 0.32	7.46	25.66	0.50
2.	3	70.09 ± 0.31	10.18	49.02	0.90
3.	5	82.79 ± 0.33	12.03	59.99	1.38
4.	10	98.68 ± 0.29	14.34	75.36	2.36
5.	20	99.76 ± 0.24	14.50	87.29	2.50
6.	30	-	-	-	-

*All the values were expressed as a mean ± SD, n = 3

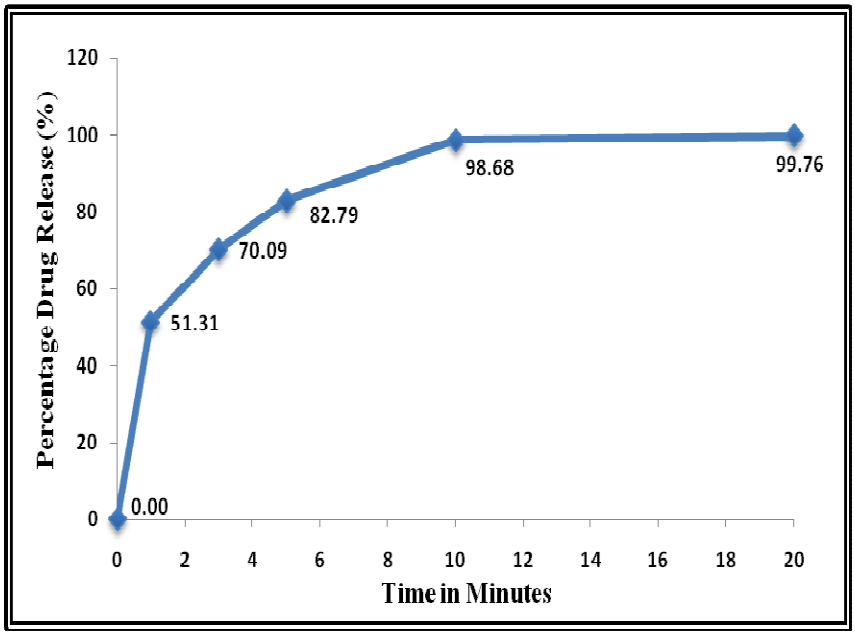


Figure 8.19 In-vitro percentage release of formulation FT8

Table 8.19 In-vitro release profile of formulation FT9

S. No.	Time (minutes)	Percentage Drug Released (%)*	Amount of Drug Released (mg)	Dissolution Efficiency (%)	Mean Dissolution Time (minutes)
1.	1	50.79 ± 0.27	7.38	25.40	0.50
2.	3	69.71 ± 0.28	10.13	48.64	0.91
3.	5	82.53 ± 0.28	11.99	59.63	1.39
4.	10	98.81 ± 0.28	14.36	75.15	2.39
5.	20	99.52 ± 0.03	14.46	87.16	2.48
6.	30	-	-	-	-

*All the values were expressed as a mean ± SD, n = 3

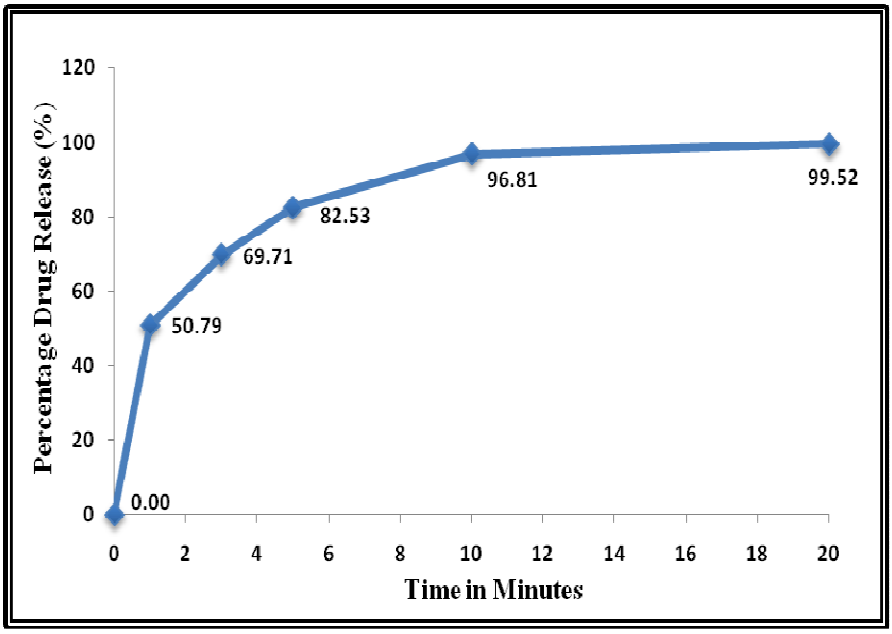


Figure 8.20 In-vitro percentage release of formulation FT9

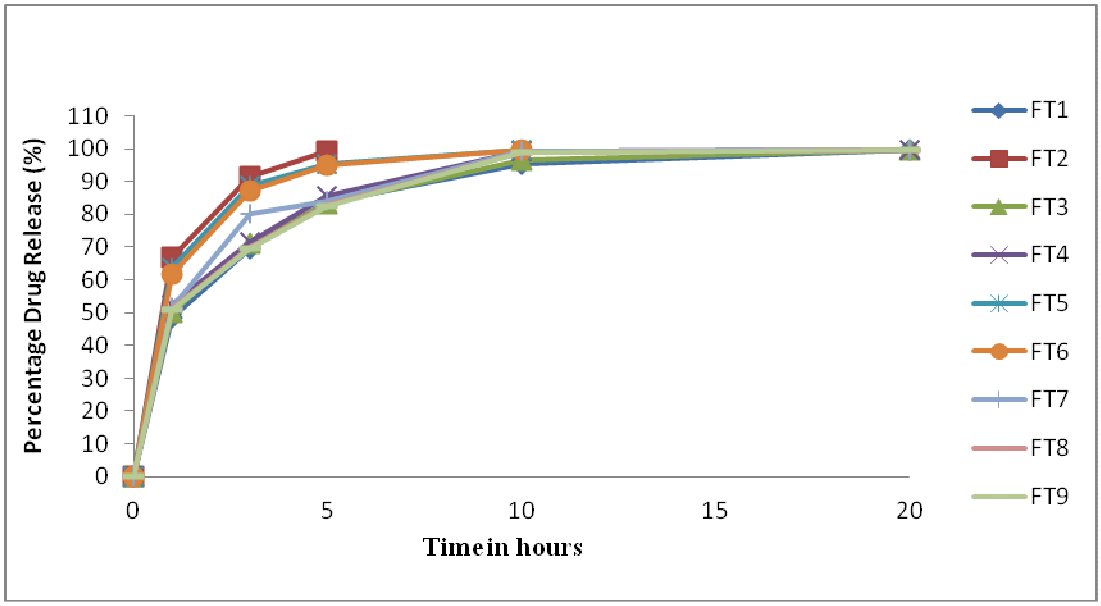
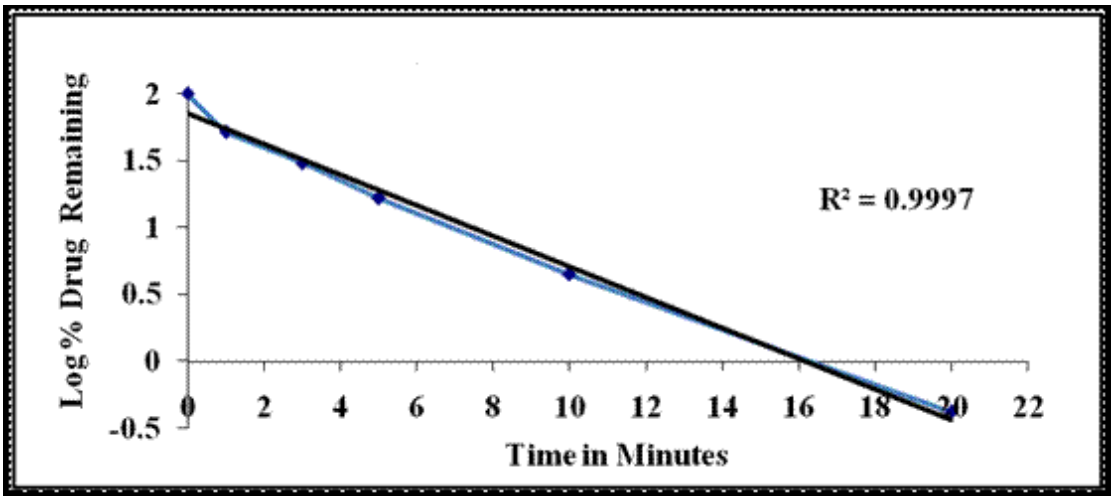


Figure 8.21: In-vitro percentage release of all formulations (FT1-FT9)

The drug release of formulation FT1,FT3,FT4,FT7,FT8 and FT9 were found to be above 99% at 20 minutes as the formulation contains average ratio of sublimation agents and the pores are formed superficially but in case of formulation FT2 good ratio of camphor was added as a perfect sublimation agent compared to all other sublimation agents which showed pores over the whole tablet influencing the release of the FT2.In formulation FT2 the pores formed highly influence the drug release as at the onset of 5 minutes the release was found to be above 99%.

8.2.8. Kinetics of *In-Vitro* Drug Release:

The kinetics of *in-vitro* drug release was determined by applying the drug release data to various kinetic models such as Zero Order, First Order, Higuchi and Korsmeyer-Peppas.



8Figure 8.22 Best Fit Model (First Order) of Formulation FT1

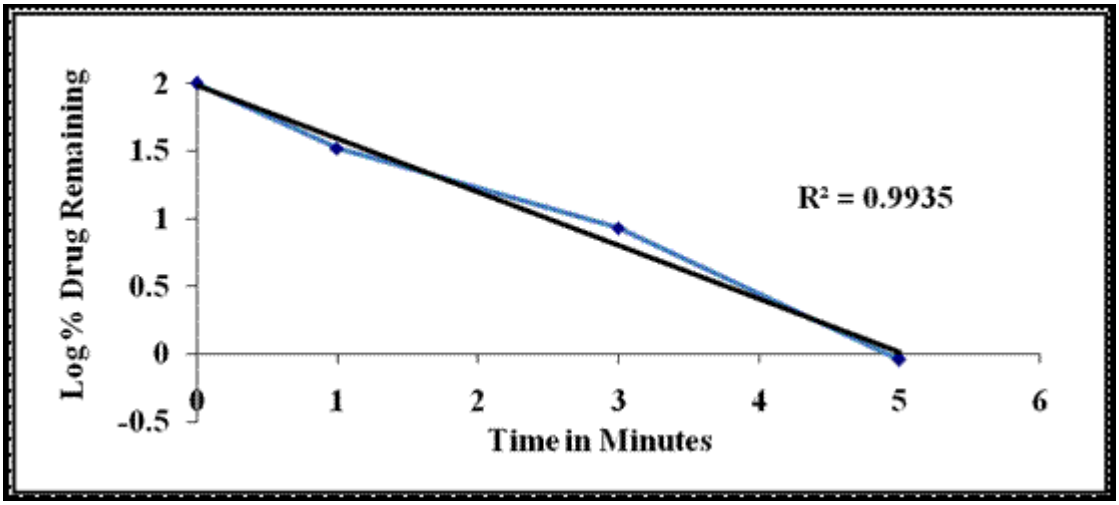


Figure 8.23 Best Fit Model (First Order) of Formulation FT2

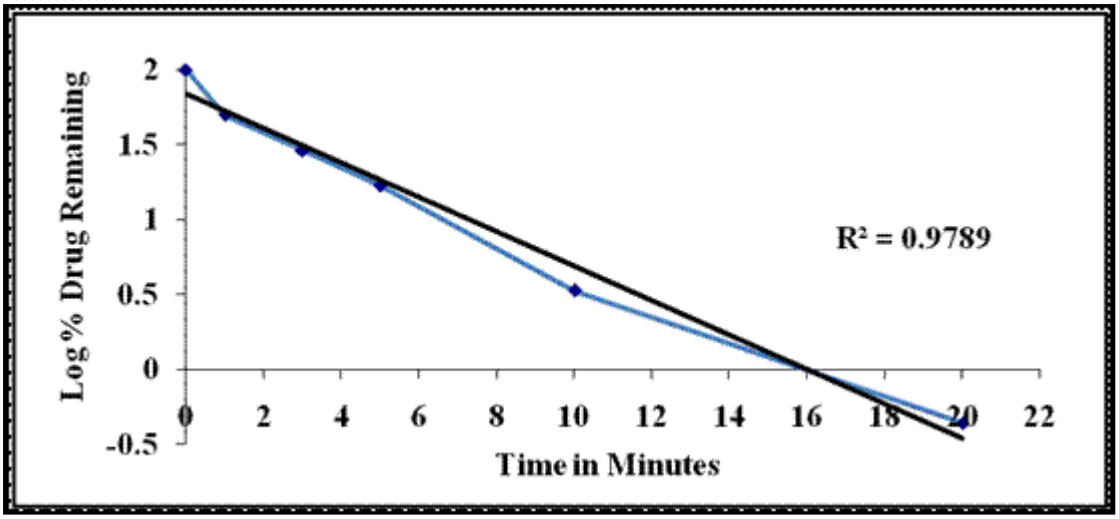


Figure 8.24 Best Fit Model (First Order) of Formulation FT3

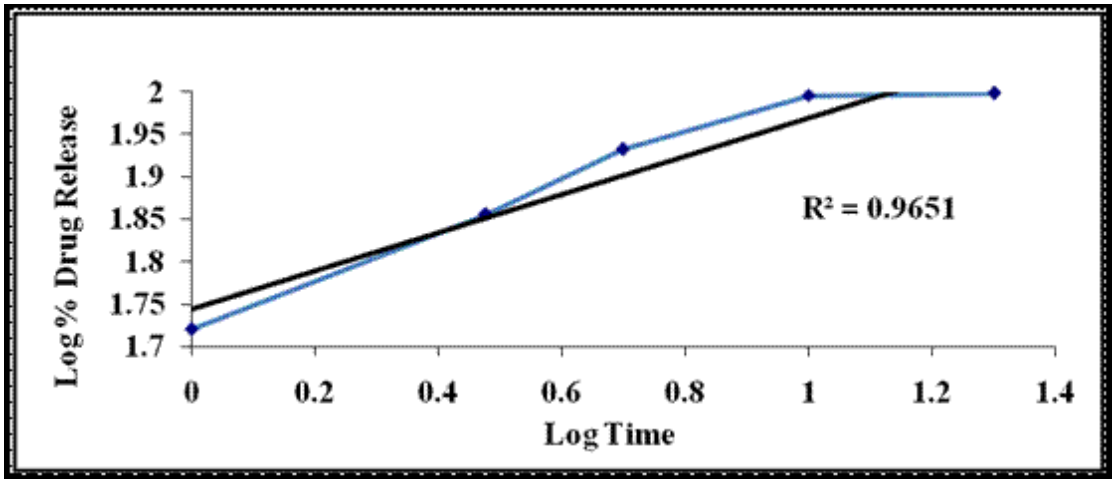


Figure 8.25 Best Fit Model (Korsmeyer Peppas) of Formulation FT4

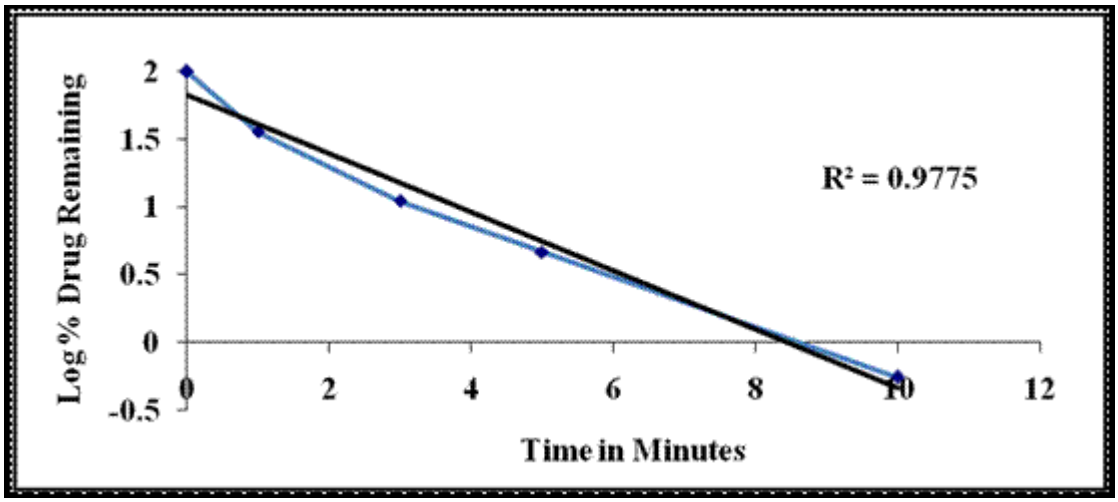


Figure 8.26 Best Fit Model (First Order) of Formulation FT5

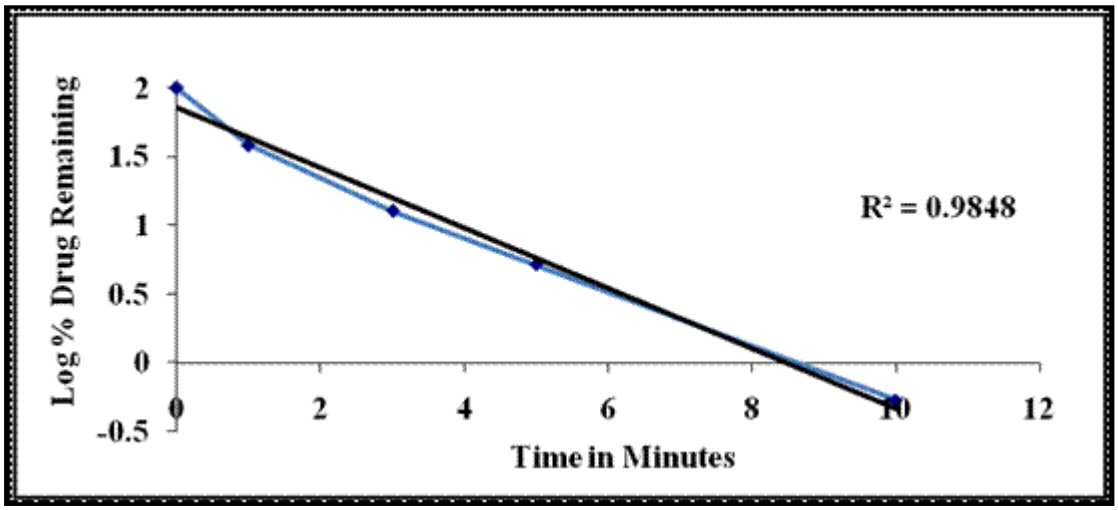


Figure 8.27 Best Fit Model (First Order) of Formulation FT6

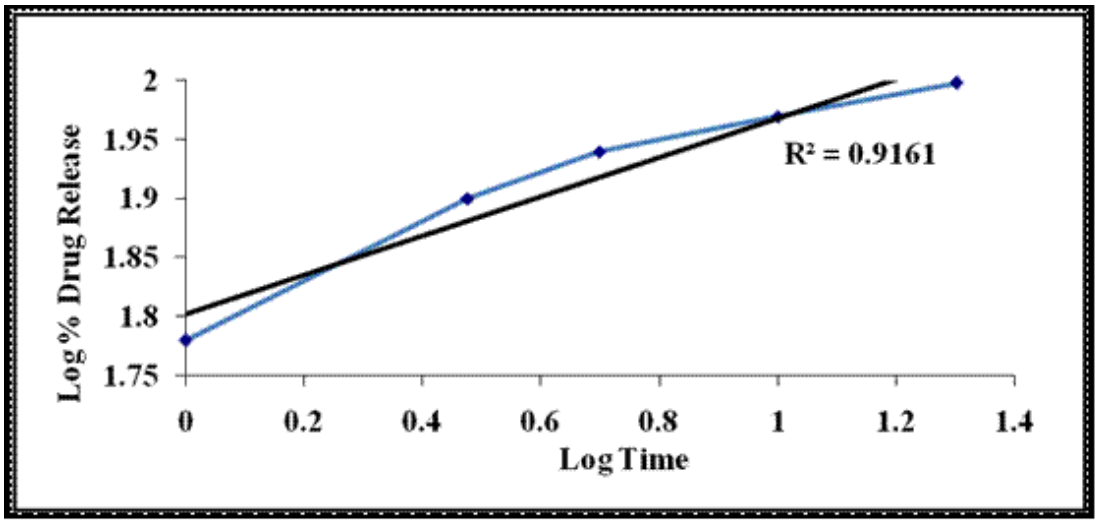


Figure 8.28 Best Fit Model (Korsmeyer Peppas) of Formulation FT7

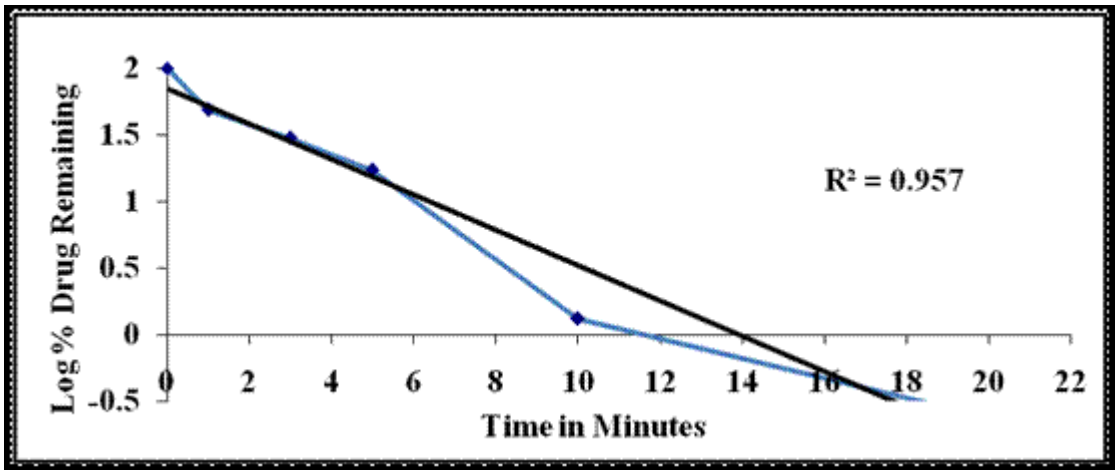


Figure 8.29 Best Fit Model (First Order) of Formulation FT8

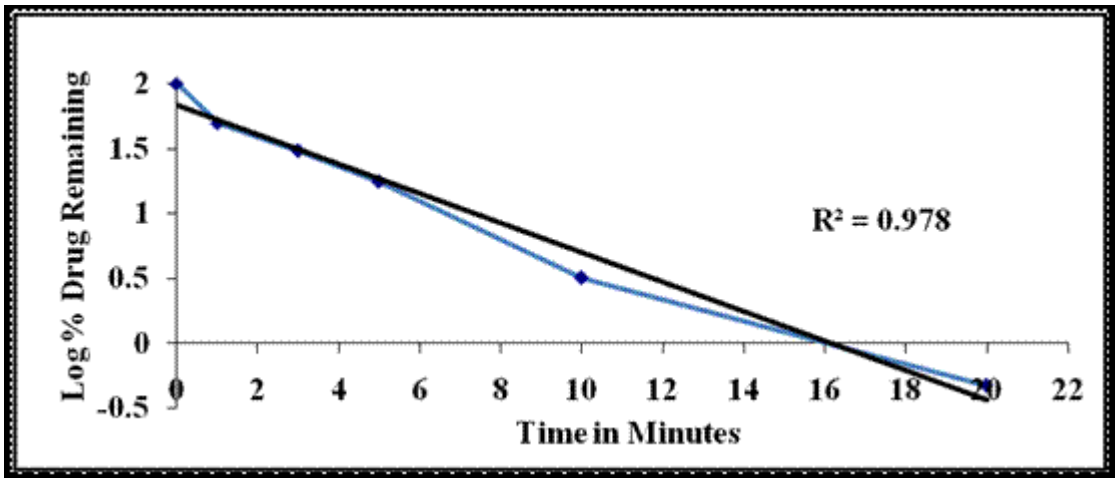


Figure 8.30 Best Fit Model (First Order) of Formulation FT9

From the kinetic data given it was observed that all prepared formulations except FT4 and FT7 were shown first order release, where as FT4 and FT7 were followed the Korsemeyer peppas model.

It was also observed that highest correlation was found for first order log % drug remaining versus time ($R^2 > 0.99$), which indicates the drug release dependent on the concentration of dissolved species.

The first order release also states that the drug dissolution in dosage forms such as those containing water-soluble drugs in porous matrices. So it was evident for the present prepared formulations.

8.3. STABILITY STUDY:

Stability Study of porous Tablets:

After exposure to accelerated stability conditions the formulation FT2 was analyzed for various evaluation parameters including general appearance at one month sampling interval. The results were depicted in Table 8.20

Table 8.20 Stability Studies of porous Tablet Optimized Formulation FT2

Characteristics	Initial	1st Month	2nd Month	3rd Month
Hardness (kg/cm^2) **	2.10±0.020	2.10 ± 0.37	2.10 ± 0.25	2.09 ± 0.20
Assay (% w/w)*	99.47±0.4	98.13 ± 0.12	98.06 ± 0.10	98.04 ± 0.10
Disintegration Time (s)**	7.83 ± 0.52	8.83 ± 0.04	8.83 ± 0.94	9.33 ± 0.75
Simulated Wetting Time (s)*	9.00 ± 0.00	10.66 ± 0.57	10.66 ± 0.57	11.33 ± 0.57
Time (minutes)	Percentage Drug Release of losartan potassium from porous tablets (%)*			
	Initial	1st Month	2nd Month	3rd Month
1	66.94 ± 0.29	65.93 ± 0.19	65.58 ± 0.10	65.39 ± 0.11
3	91.50 ± 0.34	90.23 ± 0.08	89.93 ± 0.10	89.27 ± 0.56
5	99.09 ± 0.63	98.38 ± 0.19	98.16 ± 0.11	97.93 ± 0.07

*****and ******All the values were expressed as a mean ± SD, n = 3 and n = 6 respectively

There were no characteristic changes observed in the color, surface (general appearance) at the end of three months when stability study was performed.

SUMMARY AND

CONCLUSION

9.SUMMARY AND CONCLUSION

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, least sterility constraints and flexibility in the design of the dosage form. Fast dissolving tablets has fast on set of action generally, in the present study sublimation technique was adopted as pores were formed in the tablets which reduces disintegration time. Losartan potassium has bitter taste and the taste was masked using sweetening agents. Losartan potassium plays a major role in treating hypertension. It acts as an angiotensin antagonist. It's the drug with lower sideffects so used widely because of its high solubility, low dose and therapeutic use in diseases, it was considered as an ideal drug candidate for the design of porous tablets.

A wide range of polymers was selected for formulating the tablets along with Sublimating agents to prepare the powder blend in 1:1 and 1:2 ratio with the active pharmaceutical agent, along with super disintegrants and sweetners. The tablets were prepared by direct compression and were subjected to sublimation.

Porous tablets:

The Porous tablet formulations were designed by using sublimating agents camphor, menthol, thymol, ammonium bicarbonate (FT1 to FT8), only super disintegrant without sublimation agents(FT9). Other excipents a like Avicel, Talc, Magnesium stearate, Crosspovidone, Mannitol, Aspartame were added and flavouring agent added masks the bitter taste of the drug .

For each designed formulation of porous tablets the powder blend of drug and excipients was prepared and evaluated for different micromeritic properties like Angle of Repose, Bulk Density, Tapped Bulk Density, Hausner's Ratio and Carr's

Compressibility Index in order to know the flow characteristics and all the results revealed that powder blend showed a good flow properties and thus also suitable for direct compression. The porous tablets were prepared by sublimation technique and the prepared porous tablets were evaluated for different evaluator parameters like Thickness, Weight variation, Hardness, Friability, Assay, Content Uniformity, *In-Vitro* Disintegration Time and Simulated Wetting Time. All the results obtained from the tests are correlated with the limits and were found to be within the range. From the proposed study, the FT2 Porous tablet formulation was found to have least Disintegration Time and Simulated Wetting Time.

The total drug release from FT2 formulation in p^H 6.8 phosphate buffer (dissolution medium) was found to be within 15 minutes. While comparing with porous tablets formulations with non-porous formulation, Porous tablets prepared by sublimation technique showed faster release. Stability Study at 40°C ± 2°C at 75% RH ± 5% RH for 3 months showed no significant changes. From the above parameters **Formulation FT2** was concluded as the best formulation among all the prepared Porous tablet formulations and the bitter taste was masked by using sweetening agents.

FUTURE

PROSPECTS

10.FUTURE PROSPECTS

In this work physico-chemical characterization and *in-vitro* evaluation of Losartan potassium porous Tablets were performed. The following works has to be performed in future.

1. The formulation step has to develop for the large scale production.
2. Prediction of shelf life by conducting long term stability studies as per ICH guidelines.
3. Evaluation of taste by *in-vivo* studies using human volunteers.
4. *In-vivo* release studies are also essential for development of successful formulation. So, its need to perform the *in-vivo* release studies using different animal models.
5. Establishment of correlation between the *in-vitro* and i*n-vivo* studies.

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